



# THE KIDNEY

*Medical and Surgical Diseases*



*"To connect accurate and faithful observations after death with symptoms displayed during life must be in some degree to forward the objects of our noble arts"*

From the preface to "Reports of Medical Cases Selected With a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy," by Richard Bright (Published by Longman, Rees, Orme, Brown and Green, London, 1827 )

# THE KIDNEY

MEDICAL AND SURGICAL DISEASES

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# Introduction

IN recent years there has been a resurgence of interest in the kidney stimulated in large measure by three factors: (1) an increased and refined awareness of the vital role of the kidney in the maintenance of electrolytic and fluid balances, (2) new methods of investigation of renal function, and (3) a rise in incidence of certain diseases, such as hemoglobinuric nephrosis and hypertension. It would seem mandatory when advances or, at least, changes in concepts take place in the fields of clinical medicine or physiology that they be matched by a discerning review of the related pathology. Conversely, of course, the discoveries in the field of morbid anatomy—and let us make no mistake, the reported sterility of this science is somewhat of an exaggeration—should open new avenues of physiologic investigation, or perhaps widen the old ones. For various reasons—reasons that, as a rule, are by-products of the wasteful separation of studies of structure as opposed to function—there have been long lags in both directions.

At this time, perhaps no other organ lends itself to as close a clinicopathologic correlation as does the kidney. This is so because disorders of renal functions are reflected by a great variety of physicochemical changes which can be measured or calculated with relative ease and accuracy. Moreover, in many instances, the basis for the physiologic derangements is histologically visible, and there to be properly interpreted. Undoubtedly, revised investigative methods will, in the future, yield other histologic facts. However, the principal difficulty to date is not that the pathologic changes are beyond the range of the microscope, but that there has been accumulated in the technical journals, in the texts and in the classroom a number of discrepancies concerning the histologic as well as the physiologic changes in the kidney. Into this category of contentious

pathology fall diabetic glomerulosclerosis, hemoglobinuric nephrosis, osmotic nephrosis, cholemic nephrosis, myeloma nephrosis, generalized arteriolocapillary "thrombosis," focal endocarditic ("embolic") glomerulonephritis, amyloidosis, disseminated lupus erythematosus, chronic nephrotic glomerulonephritis ("lipoid nephrosis"), "renal rickets," bilateral cortical necrosis, the renal lesions of the toxemias of pregnancy and a great many other conditions.

One reason for the discordant clinicopathologic correlation is that there is an inadequate qualitative and especially quantitative check of investigative physiologic tests with dynamic morphologic data. There are very many examples of renal dysfunction that have been speciously explained away with attractive, easily retained but obstructive histologic clichés, such as "diffuse vascular disease," "tubular amyloidosis," "calcification of tubules," "hydropic" or "cloudy swelling," "necrotic tubules," "interstitial edema," and "blockage by casts." The point about the misuse of these diagnoses is not necessarily their accuracy, but that however sparse or focal such lesions may be, they are often blamed for the entire renal disturbance.

The pathologist himself must bear much of the blame for having permitted a hyperbolic adaptation of the effective histologic data. However, the deficiency is not entirely the pathologist's, the clinical physiologists must take a modicum of the responsibility. For one thing, the facile morphologic reconstructions of renal diseases based on clearance studies warrant re-examination. No one need offer an apology for the past and ultimate usefulness and brilliance of investigations by clearance methods. However, it would be a disservice to fail to declare that, in many instances, interpretations of clearances represent a subjugation of a complicated histologic panorama to impres-

sive, meticulously quantitated, but dubiously applied physiologic data. The situation involves a rather astonishing paradox. On the one hand, physiologists eagerly report elaborate combinations of clearance tests to a decimal place. On the other hand, they feel justified in attributing acidosis, for example, to calcification of the distal convoluted tubules without attempting to determine if one, a few, or all of the nephrons are involved. Another instance of the too ready conversion of the results of physiologic tests into broad principles is the explanation of the mechanism of the anuria of hemoglobinuric nephrosis. The anuria is tenuously ascribed to necrosis of tubular epithelium in the lower portions of the nephrons, resulting in complete back diffusion of glomerular filtrate. The fact is that the extent of the necrosis in hemoglobinuric nephrosis with anuria is commonly very meager. These are just two of numerous examples indicative of the excessive divergence between histologic fact and physiologic evaluation. No less in need of reorientation is a cluster of ideas derived from questionable concepts of certain structural changes, some of which were indicated in a previous paragraph. Such a physiologic and pathologic analysis is herein attempted.

In the same spirit of trying constructively to uncloak some home truths, there is thus to be said to pathologists: it is plain\* that many pathologists feel that their function with regard to the histologic analysis of the kidney should be limited to the routine brute description of the pathologic changes. Specific clinicopathologic interpretation, they feel, is the job of the clinician. Actually there is an appreciable number of diseases that leave their diagnostic label in the kidney, a label that is clearly detectable with the microscope. Sometimes the label is a self-sufficient, specific histologic change; at other times, the definitive histologic picture is made up of a composite of changes, no one of which may establish the diagnosis until all are evaluated together. This situation, in principle, applies not only to the pathologic diagnosis of

every organ of the body, but certainly also to the field of clinical diagnosis as well. Demonstration of the proof of the validity of this thesis in renal pathology is one of the chief objectives of this book. However, the practice of this thesis certainly does not preclude the use of all accessible clinical and physiologic data by pathologists. Surely it is incumbent on the pathologist to try to integrate these data with the pertinent physiologic disorders they reflect, and thereby to give his colleagues a working interpretation of pathologic changes. The pathologist is in a pivotal position to make this integration, to fail to do so is to disregard the third dimension of the science of pathology.

With these thoughts in mind and with the added belief that the kaleidoscopic accumulation of new facts and hypotheses requires a critically purposeful inventory, this atlas and text of renal diseases was compiled. Emphasis has been placed on pathology—we trust the emphasis is on the *dynamic* rather than static, oppressively descriptive pathology. The stress is naturally so directed because the author is a pathologist, however, it happens also to be his conviction that, by this approach, proportionately relieved with *principles of clinical physiology*, the book—if it has any quality—should be of some use not only to pathologists, but particularly to urologists, internists, investigators, and undergraduate students. Toward this end, the photographs and text have been arranged in a pedagogic sequence intended for ease and clarity of presentation of individual diseases and of their differential aspects. Guided by the knowledge that the reader is at least as perceptive as the author—a rule worthy of general consideration—the unresolved problems are, for the most part, presented as if they are unresolved, rather than as if they are happily and dramatically settled. It would seem axiomatic that when there are great gaps in the evidence, it is unwise to present a situation in a lavishly wrapped package leaving the disappointing contents to be discovered in the future. On the other hand, tabulated items gathered comprehensively from the literature lose much of their usefulness unless they have been judiciously evaluated and synthesized. In this proc-

\* See Proceedings of the 13th Seminar of the American Society of Clinical Pathologists, by Baldwin Lucké and Arthur C. Allen, published by the Army Institute of Pathology, 1947.

ess of clarification, there lurks continually the hazard of oversimplification or of misjudgment. If such errors have occurred—and undoubtedly some of the conclusions are likely to provoke sharp differences of opinion—then it is hoped that they will not be attributed to a failure to hunt earnestly for the truth.

Approximately one-fifth of the photographs and a much smaller proportion of the text deal with neoplasms of the kidney. Reference to the section on tumors of the kidney is made separately because the scope of the problem is, in general, of a different order from that of other diseases of the kidney. One day this scope will be broadened when we have become equipped with the biochemical secrets of renal carcinogenesis which must expose mechanisms of prophylaxis and therapy of a corresponding biochemical character. Currently, however, the

practical problems of renal neoplasms are similar to those of other organs, namely, early diagnosis, adequate obliterative treatment, and prognosis. Attention has, therefore, been concentrated on the wide range of variation, particularly in histology, of the different tumors, and on their mode of behavior.

Much of the experience on which this survey is based was accumulated over the past fifteen years by the study of fairly extensive material during the author's association with various large institutions. In addition, many individuals have generously permitted a first-hand study of their special cases for which acknowledgment within the text is an inadequate expression of appreciation. It is felt, however, that the use made of these contributions by pathologists, clinicians, and especially students, will be a source of some satisfaction to the donors.



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# I. Embryology

THE embryology of the kidney is a rather vivid example of the principle of phylogenetic recapitulation. In its maturation, the kidney of man passes through three stages of development: (1) the pronephros, (2) the mesonephros and (3) the metanephros. The pronephros is functional as an adult organ only in the Amphioxus and in certain lampreys. The mesonephros replaces the pronephros to become the permanent kidney of fish and amphibians. In reptiles, birds and mammals, the metanephros is evolved from the pronephros and mesonephros to become the adult kidney. In the latter groups, the three kidneys develop successively, one into the other, with some overlapping in the time of appearance.

In the ontogenetic development of most of the viscera (e.g., the pancreas, the liver, the spleen) there is normally a progressive and direct evolution of the mature organ from its early fetal anlage. In the case of the kidney, the final organ or metanephros appears to develop in the most circuitous, recondite, and economically unsound fashion from the seemingly cumbersome stages of the pronephros and mesonephros. The final location and construction of the kidney bears so little gross resemblance to its anlage that it might even suggest to some a providential lapse of planning. It is hardly likely that the planning has been defective. It is more reasonable to assume not only that the excretory apparatus present at a given stage is the most efficient for that stage, but also that it is essential for the completion of the succeeding phase. Of interest in this regard is the fact that interference with the development of the pronephros and mesonephros, (e.g., cutting the pronephric duct) effects the maturation of the intermediate or final kidney. Precisely by what biochemical mechanism the pronephros "induces" the organization of the mesonephros and metanephros is a problem for the future. The chief point is that apparently purposeless fetal structures may be assumed to have functions

linked with the remainder of the embryonic economy although, at times, such functions may escape our understanding.

For reasons to be mentioned, it is of considerable conceptual significance that all three forms of kidneys have much in common in their unit of structure, even though they differ considerably in the pattern of the final tubular and vascular arrangements. The tubules in all three arise from the mesoderm of the intermediate cell mass (or its extension, the nephrogenic cord) which lies between the somatic and splanchnic layers of the mesoderm enveloping the celom. In each of these stages, the excretory apparatus includes glomeruli, tubules and a main duct. Moreover, it is remarkable to note the essential morphologic identity of the glomerulus of the pronephros, mesonephros and metanephros (plates 1, 3 and 4).

## *Pronephros*

The pronephros is the first and most cranially situated of the three kidneys. It consists of about seven pairs of segmentally arranged tubules formed as dorsolateral sprouts from the nephrotomes of the 7th to 14th mesodermal segments. One end of each tubule, a ciliated *nephrostome*, drains the celomic cavity, the other empties into a common excretory or *pronephric* duct which is formed from the union of the ventral portions of the primitive tubules and empties into the *cloaca* (plate 2). The waste products which reach the celomic cavity represent the filtrates from a tuft of capillaries, or glomerulus, formed from an offshoot of the aorta. This cluster of capillaries invaginates the celomic mesothelium to form a glomerular hillock. This glomerulus has only a thin splanchnopleural layer separating it from the celomic cavity. In other words, it does not have the Bowman's space, "parietal epithelium" or Bowman's capsule as do the mesonephric and adult glomeruli, but, otherwise, there is close structural resemblance, as

mentioned. However, the pronephric glomerulus lies adjacent to its appertaining, cuplike ciliated nephrostome, so that wastes from the blood filtered into the celomic cavity are readily sucked through the nephrostome into the pronephric tubule and drained into the common pronephric duct. The pronephric duct links the series of pronephric units (plate 2B).

Although the pronephric tubules themselves do not develop distal to the 14th somite, their collecting, or pronephric duct does grow far beyond this level caudally until it reaches and perforates the cloaca. The pronephros begins to appear in 2-3 mm embryos of nine somites (about the twentieth day) and is completed at about the stage of 23 somites (4-5 mm embryos, about 24 days). The pronephric duct reaches the cloaca shortly after this period. The pronephric duct then serves as the excretory or mesonephric duct for the following set of kidneys, the mesonephros (plate 2 D, F).

### *Mesonephros*

The *mesonephros*, or *wolfian body*, begins to appear at the level of the 14th somite in embryos about 24 days old. The tubules extend cephalically a few somites to overlap the pronephric tubules and reach their caudal limit at the second lumbar segment (26th somite) when the embryo is 7-8 mm in length (five weeks). The mesonephros and the pronephros arise from the same general source, the region of the nephrostome, or intermediate mesoderm, which appears as a continuous bridge between somites and is therefore known as the *nephrogenic cord*. The mesonephric tubules which arise from the nephrogenic cord do not tend to correspond to body segmentation, two or three, or as many as nine, may occupy the distance of one somite.

The nephrogenic masses hollow out into S-shaped tubules. One end of the tubule communicates with the original pronephric duct, now the *mesonephric* or *wolfian excretory duct*; the other end does not open into the celomic cavity by way of a nephrostome as does the pronephros, but, instead, cups itself about the knot of blood vessels, or glomerulus, which, together with the invaginated tubular capsule, constitute the *mesonephric corpuscle*.

The blood vessels of the glomeruli, as in the pronephros, arise from arterial twigs coming ventrolaterally off the aorta. The glomerular efferent vessels break up into a plexus of peritubular anastomosing venous sinusoids which empty into the posterior subcardinal veins and comprise a renal portal system. At this stage the mesonephric tubule is differentiated into a thicker proximal secretory segment and a thinner collecting segment which empties into the mesonephric duct.

The enlarging line of mesonephric tubules bulges ventrally into the celom so as to produce a longitudinal *urogenital ridge* for a distance of 15 somites on each side of the dorsal mesentery. Very shortly this fold becomes subdivided into lateral mesonephric and medial genital ridges.

After the fourth week, the cranial mesonephric tubules undergo degeneration and new tubules are formed caudally. At the end of the eighth week, the upper five-sixths of the mesonephric body of tubules are lost, having undergone degeneration and transformation into the diaphragmatic ligament of the mesonephros. Some of the remaining tubules appear to give rise to others by budding. A maximum of about 80 pairs of tubules are formed and, of these, about 34 pairs persist to nine weeks. At this time, only about 17 pairs of tubules are functional, and in another week, they all become vestigial, although degeneration is not complete until the end of the fourth month.

### *Metanephros*

The *metanephros*, or permanent kidney of humans, arises from two different portions of the mesonephros. (1) the ureter, renal pelvis, and collecting tubules come from the distal end of the mesonephric duct, and (2) the cortex, with the exception of the collecting tubules (medullary rays) included in the cortex, is derived from the caudal end of the nephrogenic mesodermal mass (plate 2D).

Just prior to its entrance into the cloaca, the mesonephric duct bends sharply. This angle marks the site at which the metanephric hillock, or *ureteral bud* first appears, about the fourth week (5 mm embryos). In invaginating,



FIG A *Mesonephros* of a 9 mm human embryo showing well developed glomeruli and appertaining tubules. The degree of development of the glomeruli (fig B) is remarkable for its approximation of the adult kidney.

FIG B *High magnification of left mesonephros of figure A.* These glomeruli are indistinguishable from those of the metanephric or permanent kidney.

FIG C *Kidney of a 14 cm human embryo showing extension of ureteral bud into the peripheral metanephrogenic tissue which is converted into glomeruli and portions of the nephron.*

(The histologic slides, from which the photomicrographs in this book were made, were stained with hematoxylin eosin, unless otherwise indicated.)



the bud cups out the caudal tip of the nephrogenic cord, which forms a closely investing cap over the primordium of the inner, or pelvic, portion of the adult kidney. The site of attachment of the diverticulum with its intimately linked nephrogenic mass becomes elongated into a tube to form, eventually, the ureter. At the same time, the primitive kidney, or, more particularly, the caudal end of the nephrogenic mass separates from the remainder of the more proximal mesonephric tissue and, at nine weeks, comes to be at its final position retroperitoneally at the level of the mid-lumbar segment. The pelvis then sprouts numerous generations of calyces and tubules into its closely applied investiture of nephrogenic tissue until, at the time of birth, there is a maximum of 20 branchings. Most of the ramifications of the pelvic off-shoots are aggregated into the medulla in the form of pyramids, a few of the collecting tubules string out into the cortex where they are known as the *medullary rays*. The interdigitation between medullary and cortical primordia is further secured by the dipping of fingers of cortex (*columns of Bertin*) between the inverted medullary pyramids. Each pyramid and its associated cortical tissue comprise a geographic unit that is reflected on the capsular surface of the embryonic kidney by indentations known as *fetal lobulations*. These interlobular grooves, which characterize the adult kidney of reptiles, birds and some mammals, for the most part disappear in early infancy and childhood although residual traces of them are common in adults (plate 7).

#### *Linkage of Proximal and Distal Nephrons*

It has been generally assumed that the distal portion of the nephron, arising from the metanephric diverticulum, and the proximal portion, arising from the nephrogenic mesodermic cap, represent the *pari passu* development of the two separate components of the nephron which subsequently unite. It has been further assumed by many observers that the failure of the two units to unite is the dysembryogenic basis for the polycystic kidney, the cysts presumably arising from functional but closed proximal portions of the nephron. However,

detailed histologic study suggests an opposing concept which might be called the "unitary theory" (plate 6).

#### *Unitary Theory*

A study of serial sections of the various stages of fetal kidneys leads to a somewhat different impression, namely, that the metanephric diverticulum does not abruptly cease its branching with formation of collecting and distal tubules, but ramifies into the nephrogenic tissue, the active primordial, multipotent cells of which are progressively added as epithelium corresponding to the cells of the advancing tubular buds until the entire length of the tubule is formed (plates 3, 4, 5 and 6). In other words, it is not as if two separate segments of contorted tubules had their two individual lumens made one after their respective blind ends were somehow opened and joined, it is rather that a single lumen becomes elongated by the accretion to its tubular lining of cells from the peripheral nephrogenic mass made receptive to canalization by the influence of organizers. The dynamics of this process can hardly be adequately documented merely with several photomicrographs but perhaps the general thesis can be gathered from plates 1 through 6. If an occlusion were to occur in some segment of the tubule, the still functioning portion of the nephron proximal to the obstruction would become dilated with fluid. The precise mechanism of the occlusion in congenital polycystic kidneys remains to be elucidated but intratubular atresia or obstruction due to extratubular fibrosis are the two possibilities. In view of the common association of polycystic kidneys with cysts of the liver and pancreas, it is not unreasonable to assume that a similar developmental fault might be responsible for the cysts in each of these organs, rather than the failure of two separate units to be joined. An obstructive mechanism through atresia or periductal fibrosis has in its favor a common application to these several organs.

In additional support of this unitary theory of origin of the renal tubule is the basically similar mode of development of the pronephric and mesonephric tubules (as well as their glo-

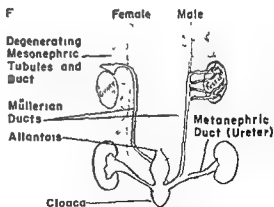
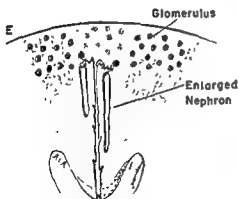
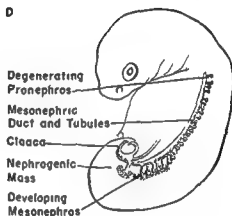
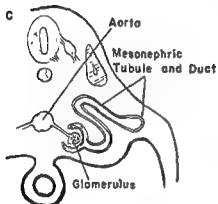
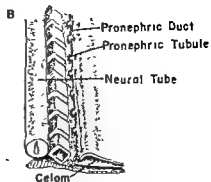
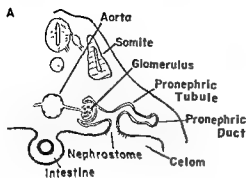


FIG A Pronephros of human kidney in section

FIG C Mesonephros in section (5 mm human embryo)

FIG E Kidney of newborn showing two nephrons diagrammatically enlarged

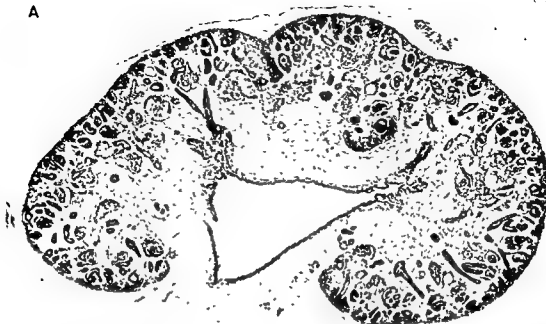
FIG B Pronephros (after Felix and Turland)

FIG D Relationship of pronephros, mesonephros and metanephros in human embryo

FIG F Relationship of genital to urinary systems, indicating the embryogenesis of vestigial structures (After Patten)

PLATE 3. FETAL DEVELOPMENT

A



B

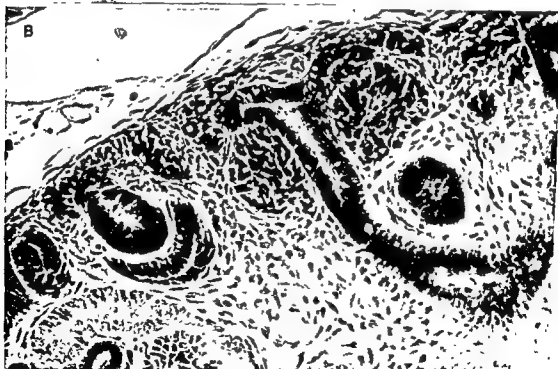


FIG A Kidney from 4 cm human fetus showing ramifications of ureteral bud to the germinal tissue at the rim. Newly formed or forming glomeruli are near the surface or at the analogous location, namely, the site of lobular fissures

FIG B Kidney from 5 cm human fetus The peripheral extension of a ramification of a ureteral bud is illustrated. The glomerulus and proximal nephron are formed not as a separate unit which subsequently joins the ureteral ramification but rather by the tubular outgrowth of the latter into the highly active and multipotent subcapsular cells



FIG. A Kidney from 5 cm human fetus illustrating the formation of the proximal portion of the nephron. The subcapsular undifferentiated cells which resemble stromal cells are converted into the epithelium of the glomerulus and proximal tubules.

FIG. B Kidney from 6.7 cm human fetus. Various stages in the formation of glomeruli from the coiled distal ramification of the ureteral bud are illustrated.



FIG A Kidney from a 9 cm human embryo. The continuous coiling of the ureteral tubular digitation into the preglomerular and proximal tubular structure is illustrated. This field indicates the initial invagination of the distal end of the coil by capillaries in the process of glomerular formation (arrow).

FIG B Kidney from a full term human fetus showing early stages in glomerular formation in the subcapsular region. This photomicrograph illustrates that the formation of glomeruli may not be completed at term, but may extend for several months afterward.

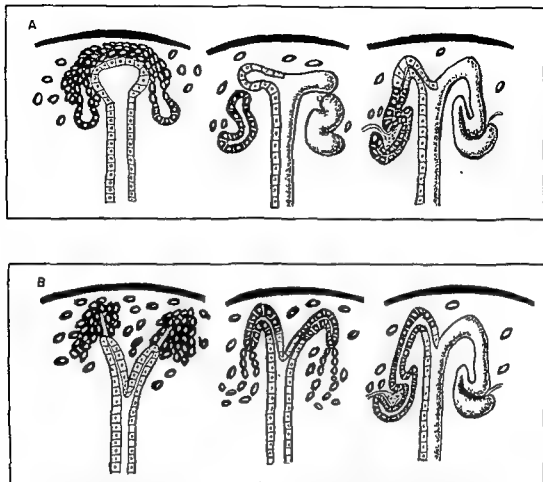


FIG. A. The current concept of the development of the nephron is that the secretory or proximal and distal portions of the nephron develop as separate histologic units after which they normally unite to form the complete nephron. Figure A represents successive stages in this development.

FIG. B. An alternative model for the development of the nephron, in which the proximal and distal portions of the nephron grow as a single unit from a ureteral bud.

ureteral bud on the metanephrogenic mass which permits growth of the convoluted nephron by progressively adding these converted epithelial cells as blocks to the pre-existing epithelial cells of the advancing tubule. In other words, it does not appear that the proximal and distal portions of the nephron grow separately with final union of their separate lumens, only a single advancing lumen appears to exist in the developing nephron rather than two distinct lumens.

meruli, incidentally). Although these tubules are not as differentiated in their functions and development as are those of the final kidney, nevertheless, they are not simple urinary conduits but carry on complicated resorptive as well as aqueductal functions. And yet, no one thinks of postulating that the glomerulus and its adjacent segment of nephron is cemented to the distal portion to complete the pronephric or mesonephric nephron. The comparison is not hyperbolic; after all, the nephrogenic cap into which the metanephric diverticulum ramifies is merely the most caudad extension of the intermediate mesoderm which previously gave rise to pronephric and mesonephric tubules. This fact is sometimes overlooked in accounting for the anlage of the proximal as opposed to the distal portions of the nephron.

#### *Development of Glomeruli*

There is no basic disagreement as to the development of the glomeruli. It should be re-emphasized, however, that the manner of origin of the glomeruli of the metanephric kidney is fundamentally the same as that for the pronephric and mesonephric glomeruli. The very end of the tubule as it lies beneath the capsule is cupped by an advancing cluster of capillaries. The inner layer of what was originally terminal tubular epithelium closely invests each of the capillaries and, together, these form the malpighian tuft. Whether or not the capillaries carry into the tuft a stromal intercapillary mesangium which survives in the adult kidney, and participates significantly in pathologic processes, is a debatable matter to be discussed further under "Anatomy" and "Diabetes." In the developing kidney, the glomeruli are progressively larger as they approach the medulla (plate 7 A). No scars of the glomeruli, which are usually stated to disappear in the early stages of development, are noted. The evidence is not satisfactory that resorption of the initial generations of glomeruli occurs.

#### *Neonatal Growth*

The total number of glomeruli that the kidney is destined to have is said to be present at birth or even prior to this time, when the fetus weighs between 2100 and 2500 Gm. This

impression seems not to be altogether correct insofar as there is evidence commonly of glomerular formation still going on in the kidneys of newborn full-term infants (plate 5 B). However, this process terminates shortly after birth.

It is estimated that about 1,300,000 nephrons are present in each kidney, although figures of various observers range from somewhat less than 1,000,000 to 4,500,000. The increase in size of the kidney that occurs with adult development results from enlargement of the various components of the nephron, particularly elongation of the tubules, rather than from an increase in the number of nephrons. It is remarkable that the glomeruli of adults have only a slightly greater diameter than those of infants, or even of the fully formed glomeruli of fetuses. However, the kidneys of larger species have considerably more nephrons than those of small species. For example, the relatively small size of the kidney of the adult rat in contrast to that of the human adult is due not merely to the larger cells and longer nephrons in the human, but to the greater number of nephrons. There are approximately 34,000 nephrons in each kidney in the rat as against about 1,300,000 nephrons in the human kidney, the average diameters of the glomeruli are about 125 microns and 200 microns respectively.

These data bear on the question of the morphologic nature of compensatory enlargement of a kidney following contralateral congenital hypoplasia or nephrectomy. The compensatory increase in size is a well known phenomenon in humans; in rats, it has been observed experimentally that after unilateral nephrectomy, the remaining kidney increases 70 per cent in weight in 40 days (Addis and Lew). This enlargement has been attributed by some to hypertrophy of the cells of the glomeruli and tubules, and by others to hyperplasia of their component cells. The correct answer undoubtedly is that compensatory enlargement is the result of both hypertrophy and hyperplasia of cells (Rollason).

#### *Vestiges*

The embryologic development of the reproductive and urinary systems is so closely allied

PLATE 7. FETAL LOBULATION

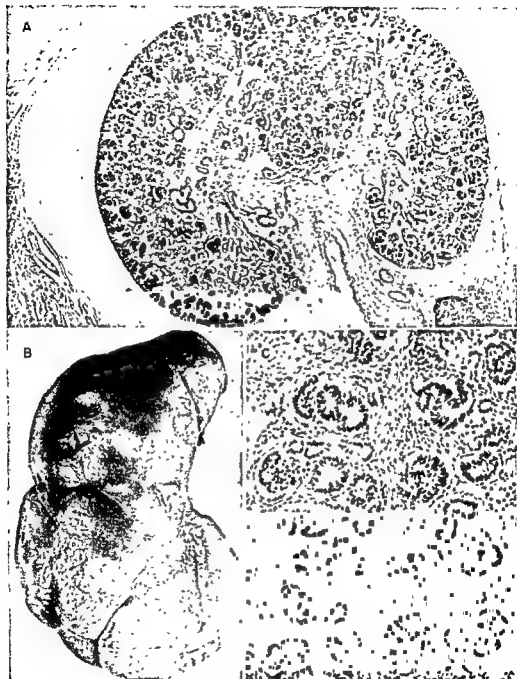


FIG A Kidney from a 67 cm human fetus illustrating a single interlobular fissure

FIG B Residual fetal lobulations of adult kidney which are commonly present

FIG C High power of fissure illustrated in figure A The glomeruli nearest the fissure are the most immature, corresponding to those beneath the capsule



that it is to be expected that vestiges of this linkage persist into postfetal life (plate 2 F) The gonads, both testes and ovaries, arise as ridges (germinal ridges) along the ventral border of the mesonephros The anatomic relationship is so intimate that the mesothelial covering of the developing gonad is immediately adjacent to and continuous with that of the mesonephros The underlying mesenchyme then differentiates into the seminiferous tubules and stroma of the testis, or into ovarian follicles and stroma

In the male, the testis economically appropriates the mesonephric (wolffian) duct as the vas deferens, and the auxiliary structures, namely the head of the epididymis, the seminal vesicles, and the ejaculatory ducts are formed from its distal portions The pronephric and most of the mesonephric tubules normally disappear by the end of fetal life Those mesonephric tubules which do not degenerate completely, comprise a cranial and a caudal group The cranial mesonephric tubules are converted into the efferent ductules of the epididymis, except for a few which form the appendix of the epididymis The appendix of the testis represents the vestigial trace of the cephalic end of the mullerian duct The entire caudal group of the mesonephric tubules becomes vestigial as the paradidymis and the aberrant ductules

In the female, an entirely new duct originates beside each of the mesonephric ducts from a pinched off cylinder of celomic mesothelium

This structure, known as the mullerian duct, subsequently differentiates into the fallopian tubes, uterus, and vagina The mesonephric tubules and ducts in the female do not persist as important structures as they do in the male However, the proximity of the mullerian duct to the mesonephros leads to certain vestigial mesonephric traces associated with the reproductive system The cranial group of mesonephric tubules and a remnant of the mesonephric duct become the *epoophoron* and *paroophoron*, which correspond to the epididymis in the male The more distal portion of the mesonephric duct (the vas deferens of the male) begins to atrophy at about the third fetal month in the female, and persists as Gartner's ducts These may be found at any level between the epoophoron and the hymen, especially along the broad ligament close to the uterus and vagina These vestigial structures may form cysts of a size sufficiently large to be clinically significant.

#### *Position of Fetal Kidneys*

There is considerable change in the position of the kidney during its fetal development. Early in embryonic life, the kidneys lie in the pelvic cavity, immediately distal to the bifurcation of the aorta From this position, they move cephalad, clearing the arterial bifurcation so that by the ninth week, they lie against the dorsolateral body-walls, and are rotated a quarter turn so that their convexities are placed laterally rather than dorsally

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## 2. Anatomy

### GROSS ANATOMY

The kidneys are situated retroperitoneally in the posterior part of the abdomen, on either side of the vertebral column and surrounded by layers of fat, fascia and areolar tissue. The upper poles of the kidneys are approximately at the level of the 12th thoracic vertebra, their lower poles border at the 3rd lumbar vertebra. The right kidney is slightly lower than the left, a circumstance usually ascribed to the limiting position of the liver. The long axis of each kidney is directed downward and laterally, the transverse axis posteriorly and laterally.

Each kidney measures about 11 x 6 x 2.5 cm, the left being somewhat longer and narrower than the right. The kidneys of the adult male weigh from 125 to 170 Gm each, those of the female weigh 115 to 155 Gm each. The weight of the kidneys tends to vary slightly with the habitus of the individual. The combined weight of the kidneys is about 1/240 of the total body weight, in the newborn, the kidneys are relatively three times as large. The weight of the kidney at different ages is about as shown in table 1 (Coppoletta and Wolbach).

### Relations of the Kidneys

The anatomic relations of the kidneys to adjacent viscera obviously differ on either side (plate 8). The left kidney is placed slightly higher than the right, presumably, so to speak, because of the hepatic barrier to the upward migration of the right kidney. The upper poles of the kidneys lie at about the level of the 7th costal cartilage (eleventh rib posteriorly) and the 12th thoracic vertebra, with the right kidney about 1-2 cm lower than the left. The lower poles of the kidney are at the level of the upper part of the 3rd lumbar vertebra.

Anteriorly, on the right, an upper segment is covered by the adrenal gland, the lower segment by hepatic flexure, and the mesial or hilar area, by the descending part of the duodenum. The largest remaining portion, laterally

between the two poles, is covered by the liver. The anterior surface of the left kidney is covered at its respective poles by adrenal gland and splenic flexure of the colon, mesially by stomach, pancreas and jejunum, and laterally by the spleen over an area almost as large as that overlain by the liver on the right. The areas in relation to adrenal, duodenum, colon and pancreas are devoid of peritoneum, the areas contacted by liver, small intestine, spleen, and, as a rule, stomach are covered by peritoneum.

TABLE 1—Weight of Kidney at Different Ages

Age	Grams	Age	Grams
Birth-3 days	13	14 months	36
3-7 days	14	18	39
1-3 weeks	15	18	40
3-5	16	20	43
5-7	19	24	44
7-9	19	24	47
2-3 months	20	3 years	48
4	22	4	55
5	23	5	60
6	26	6	68
7	30	7	69
8	31	8	74
9	31	9	82
10	32	10	92
11	34	11	94
12	36	12	95

The posterior surfaces of the kidney are in relation to muscles. This surface is altogether devoid of peritoneum, is embedded in fat and areolar tissue, and lies on the diaphragm, the psoas major, the medial and lateral lumbo-costal arches, quadratus lumborum, the tendon of the transversus abdominis, the subcostal and one or two upper lumbar arteries, and the last thoracic, diaphragmatic and ilio-lumbar nerves. In addition, the upper pole on the right rests on the twelfth rib, the left on the eleventh and twelfth. The diaphragm separates the upper renal poles from the phrenicocostal sinus, although occasionally, the muscular fibers of the diaphragm are defective

in this region in which case the pleura is in direct contact with perirenal areolar tissue

The hilar structures include the nerves, renal vein, renal artery and ureter. The latter three structures are placed in this order with the vein anteriorly, although frequently the ureter is located anterior to the vessels

### *Fixation of Kidney*

The kidneys are not as rigidly fixed to the posterior abdominal wall as is generally taught. Moreover, inasmuch as they are in contact with the diaphragm, the kidneys—and to a corresponding degree, tumors of kidneys—may move slightly with the diaphragm during respiration. Actual measurement of renal mobility with the aid of a fluoroscope revealed the range in normal adults to be from 0.1 cm to 0.5 cm (Moody and Van Nuys). The kidney and its hilar contents are surrounded by fibrofatty tissue called the *adipose capsule* which, in turn, is enclosed in the *renal fascia*. It is clear that the position of the kidney is maintained largely by the attachments of the renal fascia and the cushioning of adjacent viscera. Defects in such attachments—congenital or acquired—predispose to nephroptosis.

### *Renal Fascia*

The details of the gross anatomy of the renal fascia are still the subject of some controversy. It is generally agreed, however, that the renal fascia is a tough areolar membrane which is continuous with the subperitoneal fascia and splits into an anterior and posterior layer to invest the kidney (plate 8B). The fascia is separated from the true renal capsule by perinephric fat into which it sends fibrous trabeculae. The fat that lies behind and lateral to the renal fascia is termed the *paranephric body*. The two layers fuse superiorly with the fascia of the diaphragm. The same layers enclose also the adrenal without the formation of a complete septum between the adrenal and kidney except in rare instances. Medially, the layers blend with the areolar tissue about the great vessels at the root of the mesentery and

behind the pancreas and duodenum (Mitchell). According to Grant and most observers the fascia does not blend medially with the adjacent connective tissue, but passes in front of and behind the renal vessels, the aorta, and the inferior vena cava to join the corresponding layers of the opposite side. These features are of importance in the migration of perinephric abscesses. The posterior fascia unites medially also with the fascia of the quadratus lumborum and the psoas major. Laterally, the anterior and posterior layers fuse directly. Inferiorly, it is generally stated that the two layers do not unite but merge separately with the fascia of the iliac fossa. Mitchell, on the other hand, finds that fusion of the layers does occur inferiorly, but that the union is not as firm as it is superiorly, so that perinephric injections or accumulations of fluid (purulent exudate) may escape, particularly in the vicinity of the ureter.

### *Nephroptosis*

The diagnosis of nephroptosis as well as ptosis of other viscera is now less commonly made than formerly when it was somewhat in fashion. Part of the reason for the reluctance to make the diagnosis is, first, the improvement in diagnostic methods, and, second, the realization that the kidneys normally are characterized by a degree of mobility or "floating," which is of the range of 0.1 to 0.5 cm (Moody and Van Nuys). Nevertheless, occasional cases with symptoms proved to be produced by abnormal renal mobility do occur. These symptoms include lumbar or abdominal pain, rarely simulating Dietl's crisis (intense pain, vomiting, collapse) because of angulation or torsion of the ureter. Fatigue and gastrointestinal symptoms are mentioned prominently, albuminuria of the orthostatic variety may occasionally occur in nephroptosis, as may urinary stasis with infection.

### *Etiology of nephroptosis*

It is recognized that the kidney is maintained in its normal position by the vascular attachments of the pedicle, the adjacent

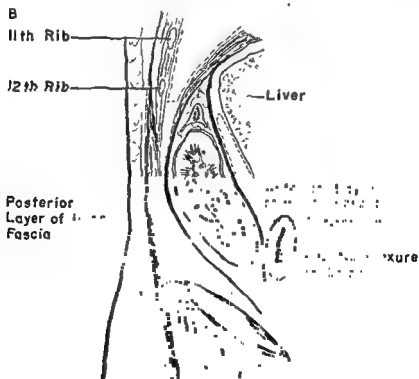
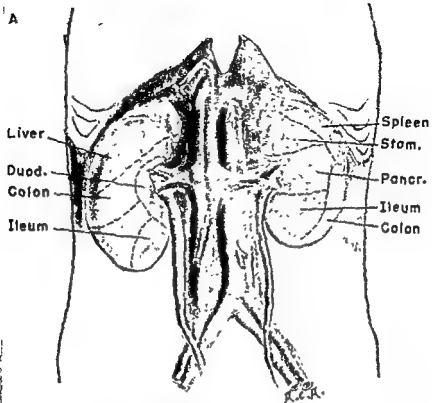


FIG. A Relation of kidneys to viscera (Anterior view) : FIG. B Renal fascia Sagittal view (After Gerota)

fascias, fat, and peritoneum, the support of neighboring organs, and the intra-abdominal pressure afforded by tonus of abdominal and back muscles. Hence, anomalies, local trauma, body habitus, emaciation, improperly supporting corsets, pregnancy, retroperitoneal tumors or other masses (which, having displaced the kidney, at times to extreme positions (Greene), are subsequently removed), and cystocele with consequent elongation of the ureters, all predisposed to nephroptosis. An observation recently made by Herbst is that in a number of cases of nephroptosis, unrelieved by nephropexy, the reason for the unsuccessful therapy was an abnormal, posteriorly located pelvis.

## MACROSCOPIC STRUCTURE OF THE KIDNEYS

### *Capsular Surface*

The kidney is enclosed by a thin, translucent fibrous capsule which may easily be stripped off. A variable number of capsular blood vessels (veins and arteries), with caliber often as great as 2-3 mm., penetrate the capsule into the renal parenchyma so that when the capsule is removed, these vessels are torn. The adipose capsule is cleanly separable from the renal capsule unless bound to it by adhesions from chronic perinephric inflammation (plates 25 A, B, and 167 A). Similarly, the renal capsule may be thickened and densely adherent to the capsular surface of the kidney as a result of parenchymal scarring following vascular disease and nephritis of various kinds. The capsular surface of the kidney is normally light purple-red and smooth, except for the fairly frequent persistence of the fissures of the original fetal lobulations. The stellate veins are usually clearly visible on the surface and tend to arrange themselves along the lines of the persistent or obliterated lobular markings (plate 50 A). Inflammations and degenerations pit and scar the surface and alter its normal coloration often in a pattern which, by itself, suggests the pathogenesis. Petechial hemorrhages may indicate malignant nephrosclerosis (plate 211), acute diffuse glomerulonephritis (plate 54), focal endocarditic glomerulonephritis (plate 85 A), or a hemorrhagic diathesis. Occasionally, casts of hemoglobin in the distal

convoluted tubules simulate hemorrhages grossly (plate 167 A).

### *Hilum*

The *hilum* of the kidney expands into a *renal sinus* which is lined by a continuation of the capsule, and which contains the pelvis, calyces, vessels and nerves embedded in fat (plate 9). The amount of fat is variable, and is dependent on the degree of atrophy of the kidney and somewhat on general obesity (plate 278 C). The fatty overgrowth (lipomatosis) may be so extensive as practically to replace the kidney. The renal pelvis—the funnel-shaped expansion leading into the ureter—is formed by the union of three major calyces, which in turn represent the junction of about twelve minor calyces (plate 11). The terminations of the minor calyces are cup-shaped, fitting snugly about one, or occasionally two or more, papillae, in a manner that permits efficient collection of the droplets of urine from the ostia of the papillae. Spirally arranged muscles about the calyces are regarded as having a milking action on these tubes, thereby aiding the propulsion of the flow of urine (plate 11 B, C).

### *Sectioned Surface*

The sectioned midvertical surface of the kidney reveals a peripheral cortex and inner medulla (plate 9). The adult cortex averages 4-6 mm. in thickness, is reddish-brown and arches over the inverted bases of the pyramids except where it alternately dips between the pyramids as the *columns of Bertin*, which extend to the renal sinus. The cortex is characteristically thickened in acute diffuse glomerulonephritis, chronic glomerulonephritis with edema ("lipoid nephrosis"), hemoglobinuric nephrosis and amyloidosis. In the nephrotic syndrome of whatever cause, the cortex tends not only to be thickened, but to be colored yellowish because of the tubular lipid principally. Wedge-shaped, pale, greyish-white cortical areas often represent foci of acute or subacute pyelonephritis. An excessively edematous sectioned surface is frequently noted in acute glomerulonephritis, acute interstitial nephritis, hemoglobinuric nephrosis and cho-

# PLATE 9 ANATOMY

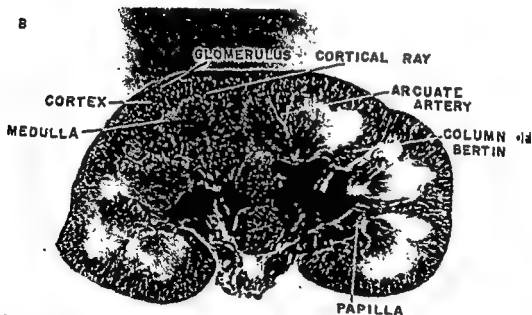
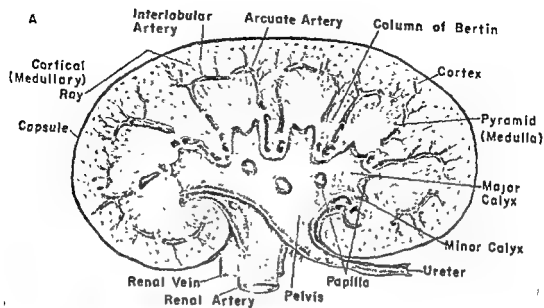


FIG A Longitudinal section of the kidney (Drawn after Brödel in Kelly and Burnam's *Diseases of the Kidneys, Ureters and Bladder*, New York, Appleton-Century, 1922)

FIG B Longitudinal section of the kidney

lemic nephrosis, in the latter instance, the icteric staining of the kidney may be apparent.

With careful examination, particularly under oblique light, the glomeruli may usually be seen as purple-red dots which appear slightly elevated from the surrounding surface (plate 10). Estimations of variations in size and color of the glomeruli as well as of the remainder of the sectioned surface, frequently afford some clue as to the nature of the pathologic processes. For example, in most forms of acute diffuse glomerulonephritis, the ischemic glomeruli are enlarged and greyish-white, in sicklelema, the glomeruli are obviously congested (plate 270).

The medullary substance is made up of 8 to 18 renal pyramids (of Malpighi), each measuring about 1.5 cm. in length and 0.5 cm. across the base. The collecting tubules, for most of their length, are located in the pyramids, but extend into the cortex as striations or medullary rays (of Ferrein). The loops of Henle are also included in the medullary rays which represent longitudinal sections of these loops, the collecting tubules, and the peritubular capillaries. Congestion of the radiating peritubular capillaries and the vasa recta is particularly conspicuous in hemoglobinuric nephrosis. The apices of the pyramids are the renal papillae which project into the lumens of the minor calyces. The base of the pyramids delineate cortex from medulla and, at this level, the arcuate artery is seen in cross section, or in longitudinal section arching over the base. The pyramids can be subdivided into units called renal lobules, of which there are about 20,000 in each kidney.

### *Renal Lobule*

The nomenclature of renal vessels implies the existence of renal lobes and lobules. Actually, there is a difference of opinion as to what precisely constitutes a lobe or lobule. By one definition, a lobule is made up of the wedge-shaped area extending from its apex in the papilla to the cortex. It includes fused collecting tubules distally and fans out toward its base in the cortex to take in a medullary ray and surrounding renal corpuscles and convoluted tubules, with the interlobular artery

at the periphery. The other point of view places the interlobular artery in the core of a lobule so that the interlobular artery would be called intralobular by those who prefer this definition of a lobule.

### **HISTOLOGIC APPEARANCE**

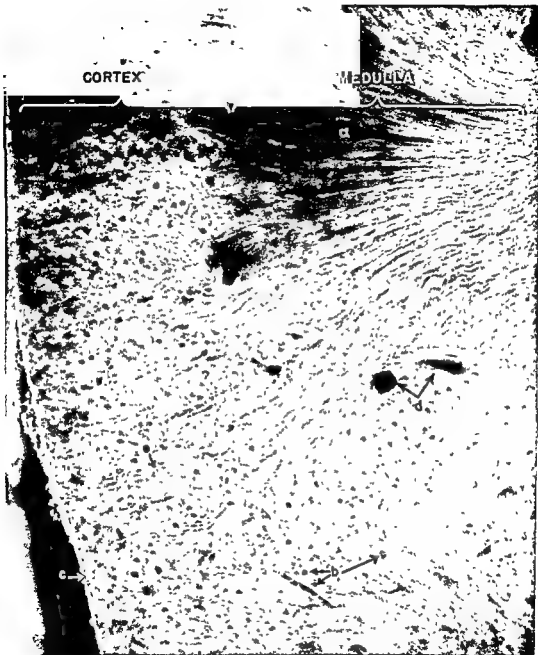
The nephron consists of the glomerulus, the so-called secretory portion of the tubular system extending through the distal convoluted tubules, and the excretory or collecting portion (plate 12 A).

### *Glomerulus*

The glomerulus, or renal corpuscle, averages 200 to 250 microns in diameter and approximately 0.0042 cu. mm. in volume. The total number of glomeruli has been variously estimated at from less than 1,000,000 to 4,500,000 (Verney) in each kidney, but the most generally accepted estimate is about 1,300,000 (Moritz and Hayman). The surface area of the loops of the glomerular capillaries in both kidneys is in the vicinity of 1.56 square meters. The glomerulus consists of Bowman's capsule and the malpighian tuft (plate 12 B). The capsule is composed of a parietal and visceral layer resulting from the invagination of the original epithelial vesicle, the primordium of Bowman's capsule, by a tuft of capillaries. The parietal layer is lined by epithelial cells which are continuous, on the one hand, with the epithelium of the visceral layer, and on the other, with the epithelium of the neck of the proximal tubule. The parietal epithelium is usually flattened so as to resemble endothelium, but occasionally it is elevated to the level of tall cuboidal cells. Special significance has been attached to the increased height of the parietal epithelium, but this remains to be proved. Under various pathological conditions these epithelial cells become swollen with fat or eosinophilic granules, or may proliferate to form a crescentic cup over the tuft (plates 62, 63).

### *Bowman's capsule*

The parietal epithelium rests on Bowman's capsule which normally is a thin membrane possessing an affinity for stains similar to that of collagen except for its argyrophilia (plates



Section of the kidney magnified 14 times, showing cortex and medulla. Also indicated are (a) dark streaks of medullary peritubular capillaries, (b) glomeruli, (c) capsule, (d) arcuate arteries, and (e) cortical ("medullary") ray (AFIP Acc 37800)



21 A, C) The abnormal changes in the membrane consist in its becoming thickened by fibrinoid alteration, amyloid degeneration or collagen, and it may become fused with the malpighian tuft

### *Malpighian tuft*

The vascular portion of the glomerulus constitutes the malpighian tuft. At the vascular pole, or hilum of the glomerulus, the afferent arteriole invaginates the Bowman's capsule, divides into 8 to 12 convoluted capillaries, which unite again at the hilum to emerge as the efferent arteriole (plate 12 B). There is some question as to whether or not each capillary divides into a number of secondary and tertiary branches in contrast to the pattern of plate 12 B. No anastomoses between the glomerular capillary loops are known to exist. The afferent arteriole is invested with an adventitia which tapers off a short distance beyond the hilum leaving the glomerular capillaries away from the hilum stripped of this outer coat which is then reformed in the same gradual manner to envelop the efferent arteriole at its exit from the tuft. The presence of this concentration of adventitial collagen about the arterioles at the hilum, tapering toward the opposite periphery of the tuft has given rise to the impression that an arboreal mesangium exists to which clusters of capillaries are attached. In other words, it is believed by many that an intercapillary supporting tissue is present which not only supports the capillaries and binds them to each other, but also divides the capillaries into lobules. Such a conception of the tuft may seem feasible in a two-dimensional section, but it is not consonant with the three-dimensional reconstruction. The more credible evidence suggests that the tuft comprises the capillary divisions of the afferent arterioles which join to form the efferent arteriole, and that those capillaries are not held together by a mesangium, or intercapillary ligaments, but are covered normally merely by

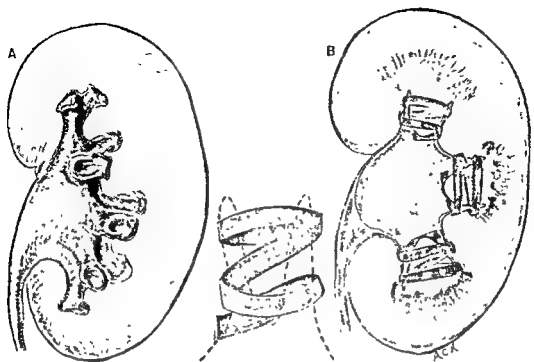
the visceral epithelium of Bowman's capsule. The sum total of the intercapillary collagen appears confined to the hilum and seems to be limited even there to the residual continuation of the adventitia of the arterioles of the vascular pole. This point of view is supported by the photographic evidence in plate 19 A.

The capillary endothelium rests on a normally thin argyrophilic basement membrane (plates 21 A, C). This membrane is easily detected in routine sections, if they are properly thin and well stained, even with hematoxylin and eosin (plate 20 A). Despite assertions to the contrary, abnormalities in the basement membrane, such as reduplication, splitting, thickening and fibrinoid alteration, may be observed with this routine stain. This fact is demonstrated in many of the accompanying photomicrographs. The point is emphasized not because the hematoxylin and eosin stain is superior to other stains for this purpose, but because there is a tendency to fail to look for fine changes in the glomerular capillaries in such routinely stained sections. The Mallory-Heidenhain stain, the Lee-McGregor, the Masson, and the silver stains are particularly adapted for the more vivid photogenic demonstration of changes in the basement membranes and for the investigation of certain qualitative reactions. With a Mallory-Heidenhain stain, for example, the basement membrane normally stains blue. Fibrinoid degenerations may be colored variously, from light orange to brilliant red, apparently depending on the degrees of degeneration. The tissue is best fixed in Zenker's solution for the Mallory, McGregor and Masson stains. The silver stains often reveal changes hidden with the Mallory or similar stains. Alterations of collagen or reticulum that may look similar in the Mallory stain may show distinctly dissimilar pictures with the silver stains. Amyloid change in the glomerulus, diabetic glomerulosclerosis, lipid alterations of the afferent arterioles, the glomerular lesions of disseminated lupus erythematosus are all

FIG A Calyceal structure. (Drawn after Brodel in Kelly and Burnam's *Diseases of the Kidneys, Ureters, and Bladder*. New York, Appleton-Century, 1922.)

FIG B Calyceal spiral muscle which on contraction empties the calyx and strips the papilla as if by a milking effect. (Drawn after Hinman, F., *Principles and Practice of Urology*, Philadelphia, W. B. Saunders, 1935.)

FIG C Photomicrograph of calyceal spiral muscle (arrow)



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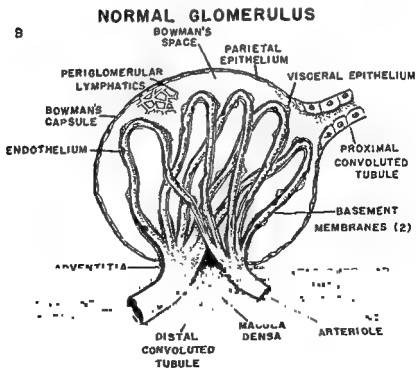
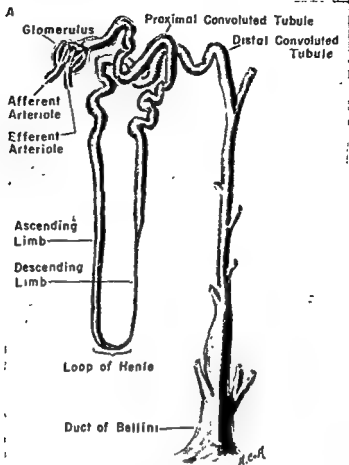


FIG. A The nephron

FIG. B. The glomerulus.

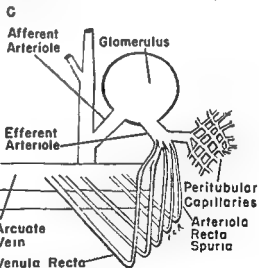
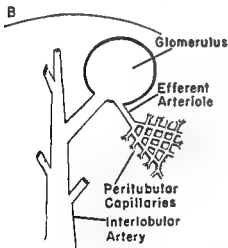
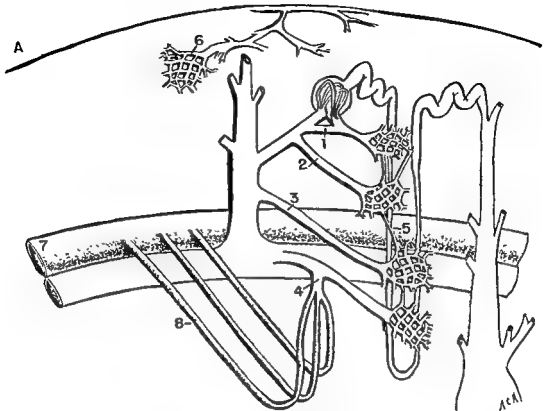
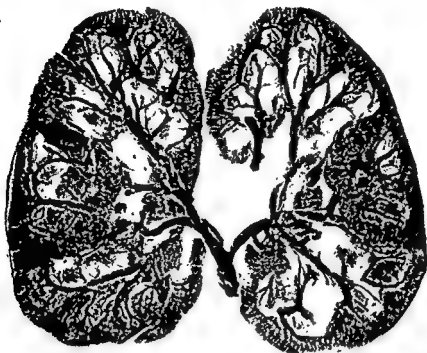


FIG A Extra-glomerular shunts viz (1) a junction between the afferent and efferent arterioles, (2) Ludwig's arteriole from the afferent arteriole to the peritubular capillaries, (3) the arteriole from the interlobular artery to the peritubular capillaries, (4) vasa recta, (5) peritubular intercapillary anastomoses, (6) anastomoses with capsular vessels. The arcuate vein (7), overlying the arcuate artery, receives the venula rectae (8).

FIG B Cortical glomerulus showing wide afferent arteriole and short, narrow efferent arteriole in contrast to the juxtamedullary glomerulus

FIG C Juxtamedullary glomerulus characterized by the relatively more prominent efferent arteriole and the vasa recta into which it empties for the most part

A

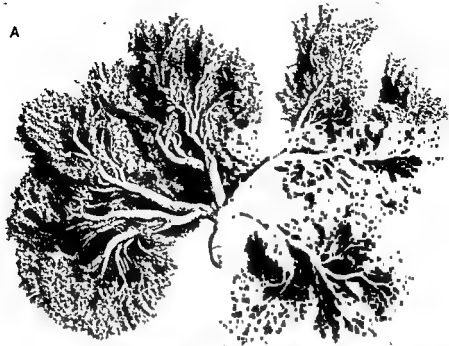


B



FIG. B The anterior surface of an entire neoprene cast shows the divisions of the largest vessels leading into a mop of the finest terminal ramifications which obscures the intermediate branches

A



B



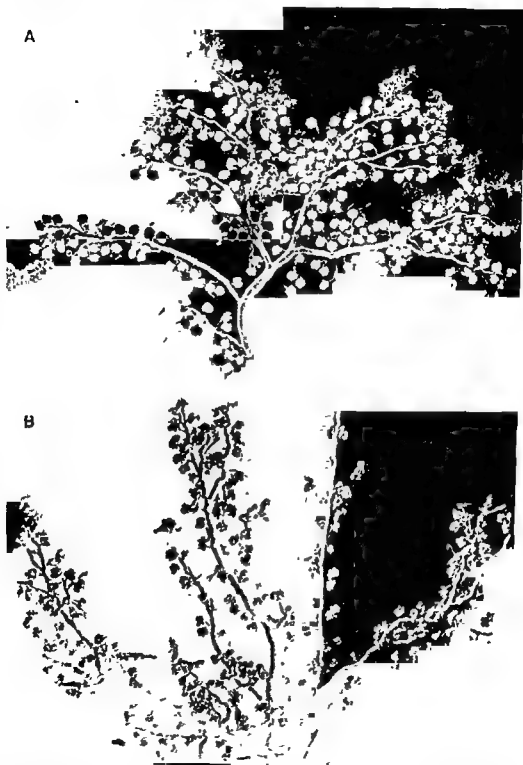
C



FIG. A. A nioprene cast of the renal vasculature separated to show the independence of the primary divisions and, in this instance, the more abundant supply to the anterior half

FIG. B. A single interlobar artery with branching arcuate, "subarcuate," and interlobular arteries along with many clusters of glomeruli

FIG. C. Wide efferent arterioles of juxtamedullary glomeruli form the straight parallel twigs of the medullary vasa recta (arterioles rectae spuriae)



FIGS A AND B "*Subarcuate*" artery with many branches (interlobular arteries) leading to afferent arterioles, glomeruli and efferent arterioles, all of which can be discerned in these photographs.

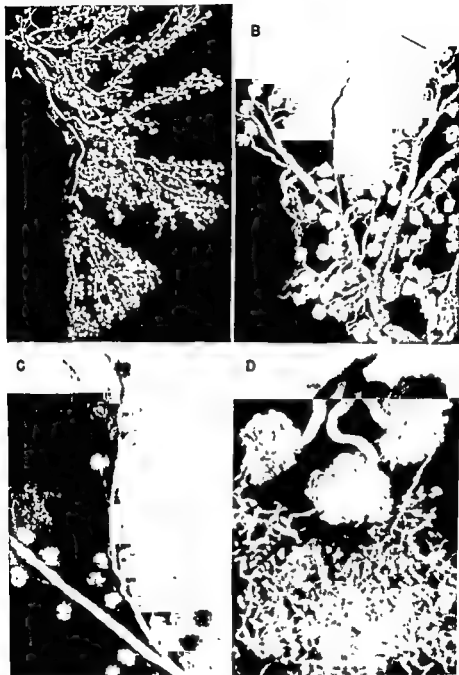


FIG. A Interlobular artery, afferent arterioles and glomeruli

FIG. C Delicate afferent and long efferent arterioles of glomeruli

FIG. B The central tapering vessel arises from an interlobular artery possibly to form an anastomosis with a capsular artery

FIG. D Efferent arterioles are seen to be of much thinner caliber than the afferent arterioles. The mesh reveals abundant intercapillary anastomoses



cases in point (plates 243, 244.). McGregor's and Masson's trichrome stains serve about the same purposes as the Mallory stains. The special advantages claimed for the periodic acid-Schiff reagent technique, except for the demonstration of carbohydrates, are not apparent.

There are variable numbers of endothelial cells visible in a plane of section, but the average is about 20. The remainder of the fixed cells of the tuft are epithelial, average about 30, and unlike the spaced endothelial cells, lie as a syncytium closely applied to the outer surface of the capillaries.

Presumably, the epithelial cells have a basement membrane of their own, analogous to Bowman's capsule (plate 12 B). This basement membrane has been described, but is most difficult to discern even with the very assiduously performed special stains. The distinction between epithelial and endothelial cells is not always possible to make, but the relation to capillary lumen, when apparent, generally identifies the cells. The evaluation of an increase of the fixed glomerular cells, as well as their enlargement and hyperchromatism is of importance in the diagnosis of certain types of glomerulonephritis. Epithelial cells chiefly, but also endothelial cells, are phagocytic, as demonstrated for example, by their retention of malaria and melanin pigment, both cells may also contain fat (plate 76). Epithelial cells may undergo hyaline droplet or vacuolar degeneration (plate 112 D).

The lumens of the glomerular capillaries contain red blood cells with a scattering of white cells. Ischemia of the capillaries, fibrinous thrombi, fused or agglutinated red blood cells, or extreme dilatation represent significant abnormalities.

*Bowman's space* is normally about 7-14 microns wide. Variations in width either through increase in size of the tuft, compression of the tuft by protein fluid in the space, or dilatation of the space as a result of increased pressure within the tubules, are changes to be evaluated. Marked shrinkage of the tufts following formalin fixation may result in misleading prominence of Bowman's space. Another variety of artefactual distortion of this space is produced by "protrusion" of proximal tubular epithelium

into it. In such "lesions," there is no evidence of stagnation of blood or other interference with glomerular circulation.

### *Juxtaglomerular apparatus*

In the arch formed by the afferent and efferent arterioles is a group of closely packed cells to which, in recent years, important functions have been assigned by some investigators (Goormaghtigh, Kaufman), although the evidence is hardly complete. These cells forming the juxtaglomerular body (pohlkissen) appear to be continuous with the muscle cells of the afferent arteriole and efferent arteriole near the glomerular hilum; they have intermingled nerve fibers and are presumed to have the function of contractility, very much as myoepithelial cells (plate 12 B). The cytoplasm may be granular or fibrillar, and the variations in cytoplasmic phase have been regarded by some observers as indicative of an endocrine function. The fibrils have been interpreted as myofibrils which regulate the caliber of the glomerular arterioles and thereby control intraglomerular pressure and filtration rate and fraction. Goormaghtigh suggests that these cells may act like the glomus cells which they somewhat resemble histologically, and shunt blood from the afferent arteriole to the efferent system, thus bypassing the glomerulus (Plate 20 C).

The juxtaglomerular body lies in contact with one wall of a distal convoluted tubule. The cells of this part of the wall, which are crowded together and have hyperchromatic nuclei, are known as the *macula densa*. The *macula densa* in combination with the juxtaglomerular body is referred to as the juxtaglomerular apparatus. The function of the *macula densa* is even less understood than is that of the juxtaglomerular body although some observers have postulated a hormonal capacity on inadequate evidence (plate 12 B).

The size and number of cells in the juxtaglomerular apparatus vary considerably even in the one section of kidney. The determination of the normal range of such variation would require extensive and laborious micrometric surveys and statistical analyses, which appear not to have been done as yet. The best such study to date indicates that the average size of



FIG. A. An afferent arteriole supplying five glomeruli.

FIG. C. Long afferent arterioles leading into glomeruli.

FIG. B. Glomeruli, afferent arterioles and interlobular artery.

FIG. D. Glomerular structure under high magnification. The details of the malpighian tuft do not suggest the presence of an intercapillary mesangium.

(These four plates of photomicrographs of neoprene casts were obtained through the generosity of Drs. R. H. Moore and G. Lyman Duff. See *Am. J. Path.* 27:95-117, 1951.)

the apparatus is 40 x 70 microns with a range of 30-40 microns x 50-80 microns (Edwards). However, correlations of the size or number of cells of the juxtaglomerular apparatus with physiologic abnormalities, such as hypertension, are plainly hazardous, inasmuch as the measurements in these conditions fail to take the normal variations into sufficient account.

### Blood Supply

#### Arterial

The renal arteries come off the aorta at an oblique angle and enter the renal hilum where they divide into a dorsal and more extensive ventral set of branches (plates 14, 15). These are "end-arteries" without anastomoses. The first branches are the *interlobar arteries* which arise in the region of the pelvic fat and extend into the columns of Bertin between the medullary pyramids. The interlobar arteries lead into the *arcuate* (arciform) arteries which are grossly visible as they curve about the base of the pyramids. These are the vessels which are likely to be involved in periarthritis nodosa and the evidence of this process may often be detected macroscopically. The next order of arteries arises perpendicularly from the arcuate arteries and extends radially into the cortex between the medullary rays. These vessels are known as either *interlobular* or *intra-lobular* arteries depending on the definition of the renal lobule,

that is, on whether or not these vessels lie within the lobule or at its periphery. Recently, the term "*subarcuate*" has been applied to the more proximal portion of the interlobular arteries (More and Duff).

The interlobular arteries, often after branching (plates 16, 17), give rise to the *afferent arterioles* which extend into the glomeruli at their vascular poles or hilum. The afferent arteriole usually supplies a single glomerulus but may supply two or even several of them. In general, that is, in the outer cortical glomeruli, the afferent arteriole is longer than and about twice as wide as the efferent arteriole. In the *juxtamedullary glomeruli* (about 15 per cent of all glomeruli) the caliber of the efferent arteriole is as great or greater than that of the afferent (Trueta et al.) (plate 13). In a given section it may be difficult to be certain of the identity of the two vessels unless by chance they are both in the same plane of section. Often the proximity of an arteriole to the interlobular artery indicates it is the afferent arteriole, inasmuch as the one arises from the other; in contrast, the efferent arteriole, after a short course, breaks up into peritubular capillaries or vasa recta, and therefore is not as likely to be in the immediate vicinity of the interlobular artery. Moreover, the presence of elastic tissue and more conspicuous muscle fibers is additional presumptive evidence that

FIG A These 2 glomeruli, enlarged 35 times, are from a case of chronic sclerosing glomerulonephritis (Addis and Oliver). In none of these glomeruli is there a trace of a suggestion of the existence of intercapillary tissue (mesangium).

FIG B *Arteriole rectae verae* arising principally from the arcuate artery to supply the medulla. One arteriola recta spuria can be seen coming off an interlobular artery. There is no indication that the arteriole rectae verae are the efferent arterioles of obliterated glomeruli as some observers believe. This kidney, including the vessels shown, was extensively infiltrated with amyloid.

FIG C Nephron from chronic sclerosing glomerulonephritis. The glomerulus is not included. The bulbous mass at the upper left is stated to have eroded the adjacent, thin, vermiform segment of the proximal tubule from a neighboring nephron. The proximal tubule abruptly dilates into its terminal portion which continues as the loop of Henle into the distal convoluted tubules, and finally into a collecting tubule.

The figures on the opposite page represent actual photomicrographs of portions of the nephron and vasculature of the human kidney, skillfully and meticulously teased apart, oriented and in-

A



B



C



(Legends on facing page)

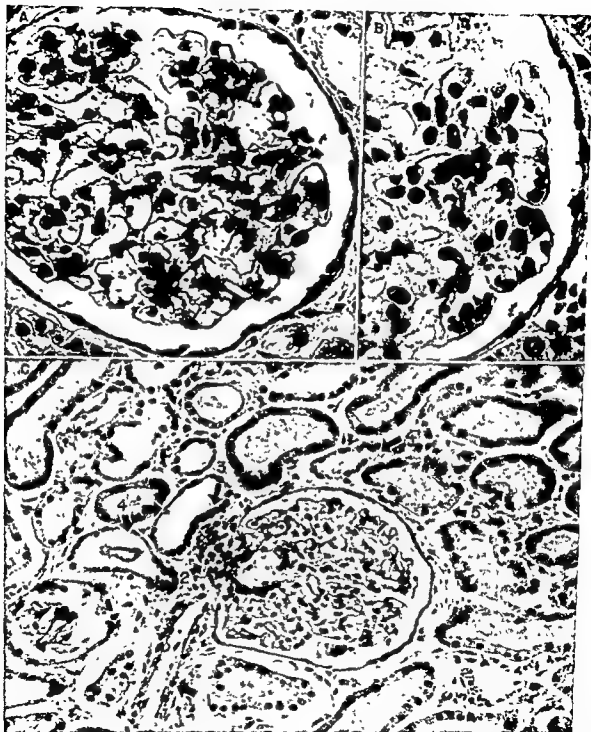


FIG A Normal glomerulus stained with hematoxylin and eosin showing capillary basement membranes, red blood cells, endothelial cells, epithelial cells, Bowman's space, Bowman's capsule and parietal epithelial cells

FIG B Megakaryocyte (arrow) within a glomerular capillary. This is a fairly common normal finding which might be mistaken for metastatic cells of a neoplasm, particularly Hodgkin's disease

FIG C Section of kidney showing glomerulus, (1) afferent arteriole, (2) juxtaglomerular apparatus, (3) macula densa, (4) distal convoluted tubules, and (5) proximal convoluted tubules

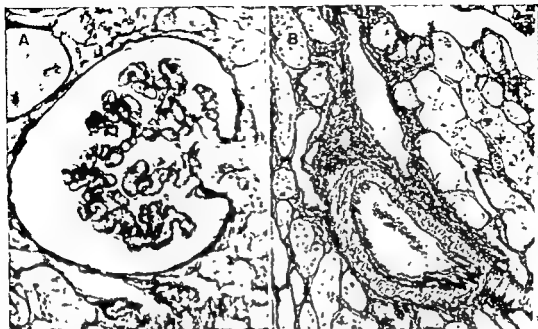


FIG. A Normal glomerulus showing argyrophilia of its capillaries and Bowman's capsule (Bielschowsky's silver stain)

FIG. B Argyrophilia of elastica of arcuate artery and vein, of tubular basement membranes and interstitial tissue (Bielschowsky's silver stain)

FIG. C Higher stain showing argyrophilia of basement membrane of tubules, glomerular capsule and some glomerular capillaries of normal kidney. This particular method of staining does not adequately demonstrate the argyrophilia of glomerular capillaries or of their lesions

the vessel is the afferent rather than the efferent arteriole. Of course, serial sections allow unequivocal identification of the vessels.

The medulla is supplied largely by *arteriolar rectae spirales* or *vasa recta* which are parallel twigs formed by the efferent vessels of the juxtamedullary glomeruli. Additional blood supply to the medulla is furnished by the *arteriolar verae rectae* which descend to the medulla as direct branches from the arcuate or interlobular arteries (plates 13, 15 C, 19 B). Some observers think that the *arteriola vera recta* is nothing more than the afferent-efferent arteriole merged as a result of glomerular degeneration. In any event, Trueta and his associates consider the *vasa recta* as the crucial intermediate pathway through which arterial blood is diverted from the cortex to the veins (*venulae rectae* of the medulla (plate 13). Evidence is being accumulated which provokes some doubt as to whether or not such a bypass actually functions, at least in dog and man (Kahn et al., Maxwell et al.).

### Veins

The veins take origin from the capillaries of the outer cortex which, by confluence, form the *stellate veins*. The stellate veins which may be seen on the cortical surface (plate 25 B, 50 A) drain into the radially arranged *interlobular veins* and thence into *arcuate veins* after the pattern of the corresponding arteries. The arcuate veins receive also the blood from the straight *venulae rectae* which drain the medulla. The arcuate veins fuse to form the *interlobar veins* which give rise finally to the renal veins (Plate 13 A).

### Collateral circulation

It is estimated that about 90 per cent of the blood normally flows through the glomeruli and that the remaining 10 per cent bypasses the glomeruli through the mechanism of shunts (plate 13 A). In other words, most of the blood in the peritubular capillary nets has less water, mineral salts and organic components than does the blood of the afferent arterioles, for example. There are five available pathways by which arterial blood may reach the renal parenchyma without traversing the glomeruli.

1. Arteriolar shunt from the afferent to the efferent arteriole.
2. Ludwig's arteriole from the afferent arteriole to the tubules, and a corresponding arteriole from the interlobular branch.
3. Anastomoses between peritubular capillaries.
4. Collateral circulation from vessels penetrating the renal capsule.
5. Arteriolar rectae from the interlobular and arcuate arteries to the medulla.

When the glomeruli or the immediately proximal portions of the afferent arterioles become obstructed, the shunts open. The extent of the extraglomerular blood supply utilized is dependent on the degree and rapidity of glomerular obstruction. The obstruction may take the form of infarcts, small emboli, glomerulitis, vascular sclerosis, or angiospasm. If the glomerular obstruction is rapid and severe, as in fulminating diffuse glomerulonephritis, the extraglomerular circulation may be inadequate to prevent necrosis of tubules. In more gradual processes, such as arteriolar nephrosclerosis, slow sclerosis of the glomerular capillaries with obliteration of their lumens leads usually to atrophy of the appertaining tubules, often with compensatory hypertrophy and hyperplasia of adjacent nephrons. Possible exceptions exist in the glomerular nephrons of the human kidney which are believed to remain functional despite the obliteration of their glomeruli. Apparently, in the instances of aglomerular nephrons, the burden of nourishment of the tubules has been adequately assumed by the extraglomerular blood supply. It is of interest in this connection that in young goosfish, the glomeruli are connected with the tubules, but this linkage is lost in the adult and the kidney becomes functionally aglomerular (Grafflin).

The pathologic changes that are to be sought in the vessels are described under the individual diseases. However, it deserves to be reemphasized that the presence of one or two histologically abnormal vessels—no matter how striking the vascular change may appear—does not necessarily prove that this abnormality was the cause of the associated renal failure. The interpretations of the arterial lesions of the typhus fevers, disseminated lupus erythematosus, and often of periarteritis nodosa bear on this obvious but frequently discounted principle.

1. Arteriolar shunt from the afferent to the efferent arteriole.

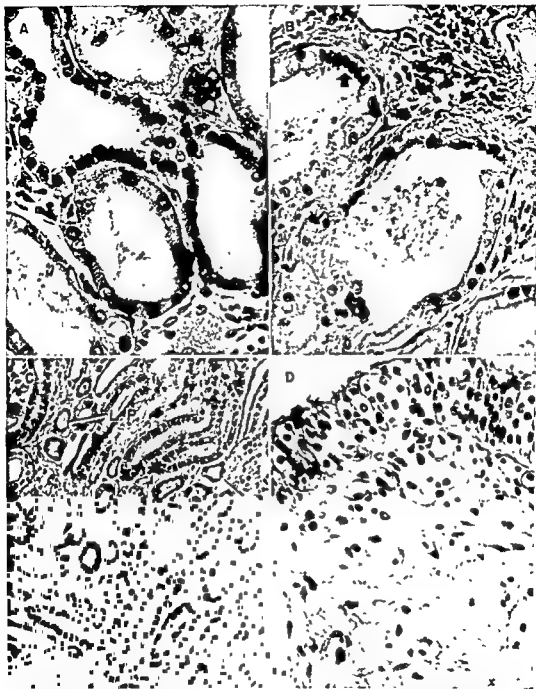


FIG A Macula densa simulated by closely packed nuclei of a distal convoluted tubule

FIG C Normal medulla showing cross sections of upper portion of descending limb of Henle, (D L), lower portion of the descending limb (L P), ascending limb (A L) and collecting tubule (C T)

FIG B Macula densa again simulated by crowded cells which are obviously in proximal convoluted tubule (arrow) and hence could not be a true macula densa

FIG D Transitional epithelium of renal pelvis



### *Tubules*

On the basis primarily of histological differences, the tubular portion of the nephron has been divided into several components (plate 12 A). In many basic respects, the structural differences are matched by differences in functional activity, as will be indicated in the chapter on physiology.

#### *Tubular measurements*

*Proximal convoluted tubule*—approximately 60 microns in diameter and 14 mm. in length.

*Loop of Henle descending limb* approximately 14 to 22 microns in diameter and 4 to 10 mm. in length, *ascending limb* approximately 33 microns in diameter and 9 mm. in length.

*Distal convoluted tubule*, approximately 20 to 50 microns in diameter and 4.6 to 5.2 mm. in length.

*Collecting tubule* about 20 to 22 mm. in length and 100 microns in width at the area cribrosa.

*Total length of nephron*—approximately 50 to 55 mm. in length (Those nephrons beginning near the medulla (juxtamedullary) are longer than those with glomeruli at the outer periphery of the cortex.)

*Total length of tubules in both kidneys* 120 kilometers (75 miles).

#### *Proximal tubules*

The proximal convoluted tubules average 14 mm. in length and 60 microns in diameter, and comprise not only the tortuous tubules of the proximal nephron, but the neck piece linking them to the glomerulus. The proximal convoluted tubules constitute the bulk of the cortex and account for the fine granularity of the gross section. These tubules are fairly easily identifiable by the characteristics of the lining cells, which are large, filled with small acidophilic granules, and lined on the luminal aspect by a brush border of cilia. The basal portion of the cytoplasm is striated by perpendicular rods which stain like mitochondria. In the superficial part of the cell, the mitochondria are granular. Beneath the basement membrane of the brush border are a pair of centrioles and what is presumed to be a Golgi net demonstrable with suitable stains. The position of the Golgi

apparatus is said to change to the infranuclear position with compensatory hypertrophy. Enzymes—lipase, acid and alkaline phosphatase—are demonstrable in the epithelium of the proximal segment; the phosphatases are also present in the distal tubules, although an abundant amount of alkaline phosphatase is localized particularly to the brush border of the proximal convoluted tubules (Newman et al.). Additional enzymes, including oxidases, dehydrogenases, deaminases, carboxylases, glutaminases, esterases, hypertensinase and others are present in the kidney.

The cells of the entire length of the proximal convoluted tubules have a similar structure, but it is apparent from the selective effects of poisons (mercuric chloride, uranium nitrate) on the tubules, and from the varying gradients of absorption of glucose and vital dyes (Oliver, 1949) that there are three or perhaps four segments that are at least functionally different.

In approximately 15 per cent of individuals over 40—and rarely in younger people—there are found isolated clusters of about five or six epithelial cells in the proximal tubules (Harman and Hogan) (plate 23 D). The cells comprising these syncytia appear as if they have become fused or agglutinated so as to resemble a foreign body giant or the epithelial reaction to the protein casts of myeloma, crystals of sulfonamides or calcium encrustations as noted in the distal tubules. These collections of cells are similar also to the macula densa of the distal tubules. The nuclei of these proximal syncytial masses are pyknotic, in contrast to the normal nuclei, but mitoses are not observed among them. They are sufficiently common to suggest that they are an indication of a degenerative change of aging with no detectable functional significance.

Of all the cells in the kidney, those of the proximal convoluted tubule are particularly vulnerable to degenerative changes. For example, in an area of early infarction, these cells may show coagulation necrosis, whereas those of adjacent distal convoluted tubules within the infarct may be preserved (plate 238 A). Similarly, the cells of the proximal convoluted tubules undergo postmortem degeneration earlier than the cells of the remainder of

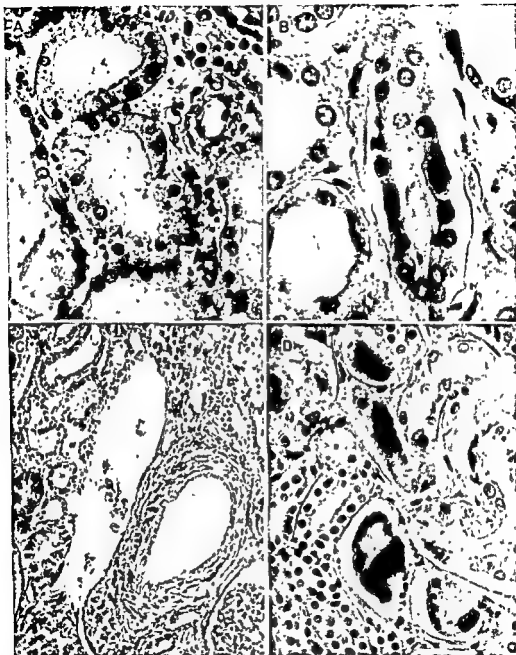


FIG. A Mitotic figure in epithelial cell of proximal convoluted tubule

FIG. C Normal arcuate artery and vein showing the intimate relation of the latter to tubules

FIG. B Mitotic figure in epithelial cell of distal convoluted tubule

FIG. D Syncytial cell masses of epithelium of proximal convoluted tubules occurring generally after the fourth decade

the nephron (plate 337 A). On this account, care must be taken not to mistake this artefact for tubular necrosis

### *Loops of Henle*

The proximal tubule continues for variable short distances (about four-fifths of the limb in the outer cortical nephrons and about one-half of the limb in the juxtamedullary nephrons) as the upper portion of the descending limb of the loop of Henle and abruptly narrows into its thin portion. The descending limb measures 11 to 22 microns in diameter and loops into the thicker ascending limb (30 to 35 microns). The transition often occurs before the turn of the loop. The length of the limbs, as indicated, varies with the position of the glomerulus, but averages about 5 mm. for the descending limb and about 9 mm. for the ascending limb. Those glomeruli near the capsular surface of the cortex have the shortest limbs and in some of these, the proximal tubules may lead directly into the ascending limb. The deeper, or juxtamedullary glomeruli are attached to nephrons with long limbs measuring as much as 10 mm. or even more and extend to the apex of the papilla.

The cells of the proximal convoluted tubule change their character abruptly in the descending limb. The brush border disappears, the cells become more flattened, the cytoplasm paler and more finely and homogeneously granular. The nuclei are about the same size and vascularity as those of the proximal convoluted tubules, but tend to be more oval, as if compressed and occupy a greater volume of the cell than do the nuclei of the proximal tubules. The free edges of the cells have terminal bars and in the supranuclear position there is a pair of centrioles with a central flagellum not visible with ordinary stains. Mitochondria are rare. A Golgi net is said to be present. The cells of the ascending portion of the limb are tall,

cuboidal or short columnar, with rather distinct cell boundaries. The base of the cell is faintly striated and appears more compact and darker than the inner, luminal portion. The nucleus is round or oval and in midposition in the cell.

### *Distal convoluted tubules*

The distal convoluted tubule measures proximately 4.6 to 5.2 mm. in length and to 50 microns in diameter. Its cells have double centrioles but do not have the cilia border. A suggestion of basilar striations may be detected. The cytoplasm is much less eosinophilic than the cytoplasm of the cells of proximal tubules. There are about five to eight nuclei visible in a cross section of the distal tubule as against the three or four of the proximal tubules. In the segment containing the macula densa there may be more than 20 nuclei in cross section. The reason for the greater number of nuclei in the distal tubule is the relatively larger amount of cytoplasm in the cells of the distal tubule as against the cells of the proximal tubule.

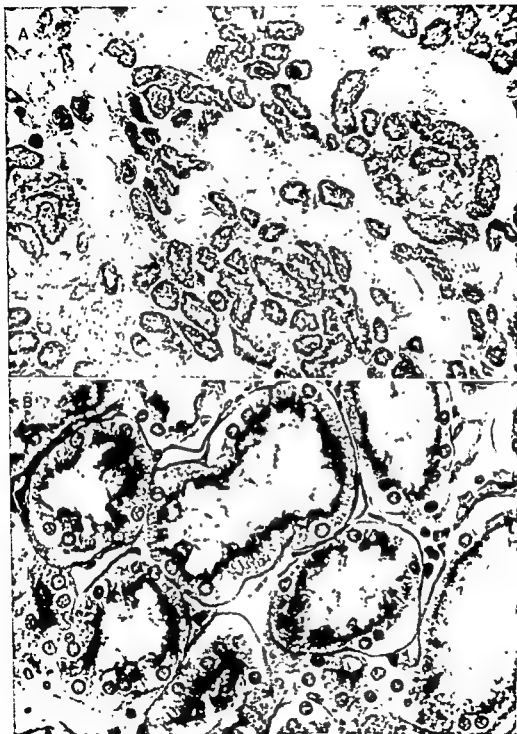
### *Collecting tubules*

The system of collecting tubules begins in the cortex with the so-called "peripheral branchings" which unite the distal secretory tubules with the excretory tubules or the medullary rays within the cortex. The medullary rays converge into the inner zone of the medulla where they join at acute angles with similar tubules. The junctions of progressively wider tubules occur at about seven levels until they end in large straight collecting tubules. These are the *papillary ducts of Bellini* which open into the minor calyces through the ostia of the *area cribrosa* of the apex of the papillae.

The epithelium of the collecting tubules differs from that of the secretory tubules. In the first part of the collecting system, the epithelium is cuboidal with sharp borders, dark stain-

FIG. A Alkaline phosphatase distribution in the normal kidney is concentrated in the epithelium of the proximal convoluted tubules. A trace is shown in the glomeruli (Gomori stain). Actually, various alkaline phosphatases, as well as acid phosphatases, are present not only in the proximal tubules, but also in the glomeruli, distal tubules, vascular endothelium and nuclei in other locations.

FIG. B Alkaline phosphatase is localized particularly to the cilia and luminal portions of the epithelial cells of the proximal convoluted tubules (Gomori stain). The phosphatase is presumed to play a role in the tubular reabsorption of glucose, as in the intestinal tract. The principle of staining is similar to that for lipase and esterase.



(Legends on facing page.)

ing nuclei and clear cytoplasm. However, as in the secretory tubules, the epithelium contains a pair of centrioles and flagellum. The cells become progressively taller through the rest of the collecting tubules, but the other cytoplasmic characteristics remain about the same. The papillae are covered with transitional epithelium similar to that of the calyces (plate 22D). The length of the collecting tubules is about 20 to 22 mm.

The *pathologic changes* that may occur in the tubules include the following:

1. hyaline droplet, hydropic and fatty alteration,
2. epithelial necrosis, regeneration and atrophy,
3. calcification of epithelium,
4. pigmentation of epithelium by hemosiderin, melanin, or lipochromes,
5. the inclusion of viruses, or simulating material, as well as bacteria, treponemas and fungi,
6. the dilatation of lumens,
7. the presence of various crystals,
8. disruption of tubular walls,
9. the accumulation of exudate and casts,
10. alteration of basement membrane by argyria, amyloidosis or collagenization,
11. neoplasia

### *Aglomerular Nephrons*

On the basis of his studies of the microdissected kidneys, Oliver has concluded that the tubules in human kidneys may function as nephrons without their appertaining glomeruli. Bell sharply disputes this conclusion chiefly on the basis of his own investigations of the kidneys, not by microdissection, but with the aid of serial sections and a great experience with a wide range of renal pathology. As far as Bell is concerned, atrophic glomeruli are associated with atrophic nephrons down to the collecting tubules. He states that there is no evidence that the small atrophic segments of tubules which persist after obliteration of the glomeruli are really functional. In the absence of more convincing proof of the *practical functional contribution* of aglomerular nephrons in the human, one cannot altogether dismiss the justification for Bell's skepticism. On the other

hand, advocates of the existence of these merular nephrons in the kidneys of human derive some phylogenetic comfort from the fact that in the toadfish, the sea horse, and the pipefish, essentially aglomerular kidneys perform abundant work and excrete most of the urinary constituents of mammalian urine.

If aglomerular nephrons do exist—and morphologic evidence of Oliver and his associates suggests that they do—it is not likely that they are totally without function. Physiologic evidence of this function is thus far lacking. However, it is reasonable to believe that the tubules of such nephrons may excrete substances brought to them by the peritubular capillaries. Perhaps, with deprivation of the glomeruli, these tubules acquire an excretory capacity that they did not previously possess. It is of interest, in this regard, that the non-aglomerular kidneys of the animals mentioned above are unable to excrete glucose, even when the blood level of this substance is raised considerably. In any event, practically speaking, it is doubtful if the aglomerular nephrons of human kidneys are of such common occurrence as to represent a significant contribution to total renal function. After all, when glomeruli become scarred, their appertaining nephrons do generally disappear or become uselessly atrophic. Although the persistent aglomerular nephron, at most, is the exceptional nephron in the kidney of humans, it would nevertheless be fundamentally informative to try to pursue Oliver's meticulous work to completion and to learn the functional properties of this type of nephron in humans.

### *Interstitial*

In the normal kidney, the interstitial tissue is hardly noticeable, particularly in the cortex. It is of the reticular type and includes a few scattered macrophages. At the apex of the pyramids, and especially about the ducts of Bellini, the connective tissue is increased in amount and tends to take on an acidophilic homogeneous character.

Pathologically, the changes include edema, cellular infiltration, lipid and crystalline deposits, amyloidosis, and neoplasia. The distribution, degree, quality and location of the

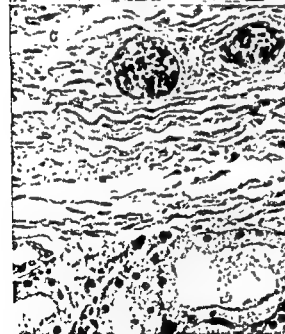
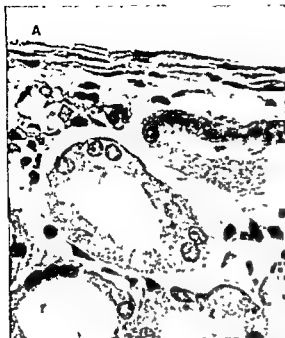


FIG. A *Residual normal capsule after stripping of the outer capsule*

FIG. C *Normal capsule, unstripped.*

FIG. B *Stellate vein anastomosing with capsular vein.*

FIG. D *Capsular artery communicating with renal parenchyma.*

edema and infiltrate varies with different diseases.

### *Lymphatics*

The lymphatic vessels are not readily seen in routine sections, but may be demonstrable by injections of dye or by the presence of metastatic deposits of cancer within the lymphatics (Rawson). Lymphatic networks are present in the capsule as well as in the renal interstitium and about the tubules. Lymphatic vessels do not seem to penetrate the glomerular tuft but rather appear to surround the Bowman's capsule very much as a net about a sphere. Usually, the lymphatic vessels about Bowman's capsule are collapsed and invisible in routine sections, unless dilated with metastases or with purulent exudate, as in some cases of acute exudative glomerulonephritis. The parenchymal lymphatic vessels communicate with the perirenal lymphatics. The larger lymphatic vessels leave the renal hilum beside the main blood vessels. Valves are found in these large lymphatic vessels but are lacking in those of the parenchyma (Peirce) (plate 51A).

### *Renal Nerves*

The nerve supply of the kidney, especially the distribution of its finer ramifications, has not been worked out completely. However, it is known that the kidneys are richly supplied with autonomic nerves extending from the 4th dorsal segment to the 4th lumbar segment, with fibers also from the vagus nerve. The autonomic (sympathetic) nerves reach the kidney with the greater, lesser and least splanchnic nerves. Fibers from the greater and lesser splanchnic nerves synapse in the abdominal and splanchnic ganglia and then make up the renal

plexus about the hilum of the kidney; the fibers from the least splanchnic nerve reach the renal hilar ganglion from which the postganglionic fibers enter the renal parenchyma. From this plexus, nonmedullated fibers extend into the parenchyma along the afferent and efferent arterioles, between the cells of the renal tubules, and on the glomerular capsule.

The nerve endings are said to be distinctive and to resemble those of salivary glands (von Smirnow). Afferent fibers also exist in the renal pelvis which, when stimulated, give rise to pain and are said to be able to cause anuria by vasomotor control. The function of the vagal (parasympathetic) fibers is not definitely known. It is clear from explantation experiments in which the kidney is removed to the cervical region, for example, and the renal artery and vein are anastomosed to the carotid artery and jugular vein, respectively, that it may function without neural connections. Indeed, in such explanted kidneys, no consistent change in either blood flow or urea clearance was noted (Rhoads et al.). This fact does not diminish the importance of the direct and indirect neural influences on the glomeruli and vessels of the intact kidneys, such as appear to occur in shock and other forms of stress. From a practical point of view, it is important to know that the related distribution of the autonomic nerves of the kidney and ureter and those of the gastrointestinal tract (splanchnic nerves, celiac and aortic ganglia) may cause lesions of the urinary tract to produce symptoms of disorders of the alimentary or biliary tract. The presenting, and sometimes the only symptoms in about 25 per cent of cases of disease of the kidney and upper ureters are nausea, vomiting, pain in the upper quadrant, constipation or diarrhea.

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# 3. Normal and Abnormal Physiology

## INTRODUCTION

THE zigzag development of our ideas on the physiology of the kidney parallels the detoured mode of advance in most fields of theoretic activity. An epochal gain was initiated by Malpighi's announcement in 1666 that the medullary striae were not really fibers, but were tubes and that they were in continuity with globular "glandular" structures or glomeruli. This conclusion was definitely proved by Bowman in 1842 with the help of the then popular method of injection of red lead. Bowman assumed that the urinary wastes reached the tubular lumens by the method of excretion through the epithelium, and that the role of the glomeruli was essentially to supply the water with which to flush these products down the nephrons. Heidenhain subsequently modified Bowman's idea slightly by maintaining that not only did the tubules secrete the urinary constituents, but that salts as well as water entered the tubular lumen through the glomerular membrane.

This concept was for a generation favored over Ludwig's theory that urine consisted entirely of the glomerular filtrate which had been concentrated by the tubular reabsorption of water through the process of simple diffusion. Ludwig's explanation did not account for variability in degrees of concentration of the urinary solids which ought to have been equal with unselective diffusion. For example, urea is concentrated about 60 times, whereas chloride is concentrated only twice. During the early part of the twentieth century, convincing evidence was brought together to form the Cushman theory of filtration-reabsorption, according to which urine was composed of the glomerular filtrate minus what was *selectively* reabsorbed across the tubular epithelium into the peritubular capillaries. Because the range of concentration of the solids of the glomerular filtrate was incompatible with simple diffusion on the basis of the known principles of osmotic pressure, it was hypothesized that some form of

"vital activity" propelled the return of essential metabolites across the tubules in spite of an adverse oncotic gradient. This hypothesis still stands.

It must be admitted that little of comparably fundamental importance has since been added to our information on renal physiology. We have learned, for example, that enzymes occur within the kidney, enzymes that are concerned with the transtubular migration of glucose and enzymes that possibly are concerned with hypertension. We have learned that the tubules may also excrete substances as an ancillary function and that the function may be measured, at least in the structurally normal kidney, by the clearance studies. We do not yet know why so tangible a process as pericarditis occurs in uremia, nor, except for the effects of hyperkalemia, precisely what is the form of toxicity in uremia. We are really just beginning to understand the vagaries of renal circulation, including, indeed, the finer anatomy, as well as the influence of shock, vasoconstriction, nervous stimulation, various hormones and therapeutic drugs. Even the mechanism of anuria following the action of nephrotoxic agents is still highly controverted.

Obversely, for the many who continue to believe that morphology long ago yielded all the important information inherent in that subject, the awareness of the gaping hiatuses that exist in clinicopathologic correlation ought to dispel such an unproductive point of view. It would be pointless to pretend that we have been clear about the physiologic pathology of the many forms of tubular vacuolization, granularity, necrosis, protein and pigment casts, juxtaglomerular apparatus, glomerular changes, and the nature of the various vascular alterations, to cite a few instances. Even the mere identification of the many crystals that are noted in histologic sections of kidneys has not been refined over the past half century. Exact knowledge of the composition of the crystals would undoubtedly furnish fruitful clues not

only about the pathogenesis of some of the renal diseases (as in cholemic nephrosis), but also information about the metabolic chain, particularly the end product, of certain materials, as is illustrated, for example, by the deposits of calcium oxalate crystals in ethylene glycol poisonings.

In the ensuing chapters, considerations of the various aspects of renal diseases will be coupled, when feasible, with discussions of the pertinent altered physiology. This current chapter is meant to serve as a basis for orientation on the general subject of renal physiology. Although much obviously remains to be worked out, and although some phases of dynamic renal physiology must be considered to have advanced a step from the dogmatic to the controversial level, there nevertheless remains a fairly solid conceptual framework on which to build.

#### GLOMERULAR FUNCTION

The kidney contributes to the stabilizing homeostatic regulation of the internal environment by three processes:

- 1 Removal by filtration of a portion of the blood plasma and its solutes (e.g., potassium, sodium, chloride, sulfate, urea, glucose, amino acids, etc.)
- 2 Selective tubular reabsorption
- 3 Tubular synthesis and excretion

The intimate and constant control of the constituents of the blood is facilitated by the fact that, at rest, 25 per cent of the cardiac output (1200 cc. per minute, or 1700 liters per day) is apportioned to the kidneys, even though they comprise only a small fraction (0.5 per cent) of the body weight. Such a disproportionate fraction of the cardiac output is made mechanically possible, in the main, by the enormous capacity of the glomerular capillaries. Of the 1700 liters or so that traverse the lumens of the glomerular capillaries during the course of a day, 170 liters, or 10 per cent, of the volume is removed from the blood in the form of glomerular filtrate. From this abundant filtrate, only about one liter of urine is formed and the remainder of the filtrate is returned to the blood by reabsorption across the tubular epithelium into the peritubular capillaries and

vasa recta. The glomerular capillaries are distinctive in (1) their location between two arterioles, afferent and efferent, (2) the level of the blood pressure (75 mm. Hg) which is approximately twice that of other capillaries, (3) their double wall including both an endothelial and epithelial basement membrane as well as epithelial cells located external to the membranes, and (4) their concern with filtration alone rather than with filtration and reabsorption as in the case of other capillaries.

#### Filtration

Glomerular filtration is the resultant of several hemodynamic forces and the organic integrity of the glomerular capillaries. The hemodynamic forces are: (1) hydrostatic pressure of the capillaries which normally averages 75 mm. Hg, and (2) the osmotic pressure of about 25 mm. Hg, exerted by the constituents of the plasma which is augmented by an intracapsular tissue pressure (or the pressure in Bowman's space) of about 10 mm. Hg. The effective filtration pressure is, therefore, normally  $75 - (25 + 10)$  or 40 mm. of Hg. An increase in the capillary pressure causes an increase in filtration pressure and hence in the filtration rate. With decrease in glomerular capillary pressure to less than 40 mm. Hg, as may occur in shock, the filtration pressure may be lowered to a degree sufficient to cause anuria. Variation of either of the two other vectors produces obvious, corresponding alterations in the filtration. For example, if the capillary pressure remains constant, an elevation of intrarenal pressure or of intracapillary oncotic pressure works in the direction of decreasing filtration pressure and filtration rate. A decrease in osmotic pressure by itself, such as may occur in hypoproteinemia, increases filtration pressure and rate. If all three factors are constant, that is, the capillary, the osmotic and the tissue pressures, then an increase or a decrease in blood flow results in a corresponding change in filtration rate.

#### Regulation of Glomerular Function

The advances in recent years in the field of renal function have been centered on the critical mechanisms of regulation of renal cir-

ulation Previously, it was apparent that the renal vessels possessed great lability in their response to chemicals or the stimulation of nerves For example, it was known that adrenalin produces vasoconstriction, and that urea, glucose, sodium bicarbonate and xanthines cause vasodilatation, that reflex stimulation of the vasoconstrictor center narrows renal vessels, and that repeated stimuli to the 11th and 12th dorsal fibers provoke vasodilatation And so, the renal response to excitement, hemorrhage, cardiac decompensation, and other homeostatic alterations was presumed to depend on this gross basis However, it is now clear that the adjustments in the circulation hinge on the most sensitive response by fine, nicely balanced, strategically placed structures. Among such structures, the efferent arterioles loom especially important

In the first place, it is a fact that the formation of urine increases with constriction of efferent arterioles and elevated renal blood pressure, and decreases in reverse circumstances. However, along with vasoconstriction (produced by adrenalin or stimulation of the reflex vasoconstrictor center of the rabbit) the volume of the kidney expands The injection of adrenalin may be demonstrated, by direct observation and measurement in the frog, to increase the size of the glomeruli and to elevate the pressure in their capillaries (Richards and Schmidt) This expansion is attributed to distention of the glomerular capillaries as a result of constriction of the efferent arterioles, with consequent narrowing of the glomerular vascular outlet and raising of the intraglomerular vascular tension It is on the intraglomerular pressure that the important function of renal filtration (and possibly even systemic blood pressure, in at least some instances) has close bearing The efferent arterioles, then, constitute the order of renal vascular ramifications that is of key significance.

It remains to be shown whether or not vaso-

due actually to the normally smaller caliber of the efferent arteriole on which slight vasoconstricting action would exert relatively greater effect than it would on the afferent vessel.

There is another differential consideration involved in the glomerular circulation. The blood in the efferent arteriole differs from that in the afferent vessel by virtue of the loss of water and other urinary constituents and the consequent increased viscosity. The possibility that some of the urinary constituents may have a vasodilating action on the afferent side of the glomerulus, prior to their filtration, is to be considered.

### *Neural Control of Glomerular Blood Flow*

From the time of Claude Bernard's contributions, it has been known that the splanchnic nerves can experimentally be shown to influence dramatically the flow of urine In dogs and rabbits, the sectioning of these nerves increased the amount of urine; stimulation of their peripheral ends causes formation of urine to stop. In animals with explanted kidneys deprived of their nerve supply, diuresis lasts for some days (Bieter). In addition, it was shown by Burton-Opitz and Lucas, that section of the splanchnic nerves increases renal blood flow, whereas stimulation of them decreases the flow. In the increased formation of urine following splanchnic section, it would seem likely that the glomeruli played a role. And, to be sure, direct observation of glomeruli of frogs during stimulation of the ipsilateral splanchnic nerve reveals cessation of blood flow through many of the glomeruli; approximately 50 per cent become inactive The afferent arterioles of such glomeruli become constricted. When the electrical stimulation is discontinued, the afferent arterioles suddenly dilate with a burst of blood flow Stimulation of the central ends of cut sciatic and vagus nerves produces similar responses Actual section of the splanchnic nerves, as expected, results in an increase in the number of active glomeruli corresponding to the increased amount of urine formed. The greater output of urine lasts for a short while until readjustments in glomerular circulation take place. Attempts to put this information to practical test by sympathetic nerve blocks have been made in cases of anuria due to hemoglobinuria (lower nephron) nephrosis, with variable results.

### Glomerular Permeability

There is reason to believe that the walls of the glomerular capillaries behave as filters and that molecules below a certain size normally seep through the "pores." It is stated (Bott and Richards) that most of the mesh surface

allows particles of 50 Ångströms to go through. In other words, substances with a molecular weight of 68,000 or less pass through the glomerular filter. For example, hemoglobin with a molecular weight of 68,000, egg albumin (molecular weight 35,000), Bence-Jones protein (molecular weight 20,000 to 30,000) and myoglobin (molecular weight 17,500) are excreted, whereas serum albumin (molecular weight 70,000), serum globulin (molecular weight 150,000) and hemocyanin (molecular weight 5,000,000) are normally retained. However, the sizes of the "pores" cannot be the entire factor determining the size of the molecules excreted; actually, there is currently being accumulated evidence that small amounts of protein\*, albumin especially, but also globulins and even fibrinogen, may normally pass the glomerular filter, subsequently to be reabsorbed by the proximal tubules. It is suggested (Addis) that, ordinarily, normal capillaries allow at least 5 mg of protein per 100 cc of blood to escape through their walls and that the glomerular capillaries are probably equally permeable. If, then, this minimal amount of 5 mg of protein passed the glomerular filter, it would yield 9 Gm of protein in the urine unless it were reabsorbed.

The detection of such small amounts of protein by microchemical techniques is said not to be possible and that, for this reason, analysis of glomerular filtrate, aspirated directly from the nephron failed in the past to reveal the presence of protein. Recently, Terry and his associates have found that they could produce proteinuria with albumin, globulin and fibrinogen in normal dogs, merely by raising the level of plasma proteins to about 9.6 Gm per cent.

\*"Albuminuria" is commonly used incorrectly in place of "proteinuria", the latter may involve not only albumin, but also globulins, fibrinogen, nucleoprotein and proteoses.

They termed this level the renal threshold for proteinuria. In other words, given a high enough blood level, protein of molecular weights many times 68,000 readily seep past the normal glomeruli of dogs.

Under abnormal conditions, the glomerular filtration is affected by changes within the walls and lumens of the glomerular capillaries. Glomerular stasis, embolization and thrombosis, inflammatory and degenerative alterations all may contribute a vector to disturbed glomerular filtration. This may occur not only by direct organic modification of the capillary walls, and, hence the permeability, but by interference with the glomerular circulation through stenosis, or by dilatation of the glomerular capillaries or arterioles. In many diseases, the interferences are of a focal, variable or even functionally neutralizing nature, involving individual capillaries (as in diabetic glomerulosclerosis, for example) so as to hinder or to make impossible the detection of their influence and localization by clearance studies.

It is further obvious that stagnation of the blood in the glomerular capillaries, as in congestive heart failure, is a hindrance to effective filtration because of the simple fact that inadequate blood is exposed to the surface of the glomerular filter. However, there is another matter to be considered which is probably important, but poorly understood, and that is the effect of the stagnation of blood on the functional integrity of the wall of the glomerular capillaries. The answer to this problem has a direct pertinence to the state of the glomeruli in a variety of disorders including shock and glomerulonephritis. The matter of altered permeability of glomerular capillaries following abnormal dilatation is an additional problem on which adequate precise data are lacking. Dilatation of other capillaries with adrenalin has been shown by Krogh to result in their increased permeability to protein so that a similar situation might be expected to exist in glomerular capillaries. In the lesion of diabetic glomerulosclerosis, the glomerular capillaries surrounding the lesion are often enormously dilated (Allen). It has been suggested that this conspicuous glomerular capillary dilatation may play a part in the loss of protein

alkalosis, is not to be regarded necessarily as the histologic cause of the disturbance in tubular control of pH, as has been done

### *Renin Formation*

An additional function of the tubules appears to be the formation of renin, particularly in ischemic kidneys, or in kidneys with reduced renal pulse pressure. Whether or not the tubules are concerned in the hypertensive mechanism by the production of certain aldehydes, the elaboration of enzymes, or the deamination of pressor amines remains to be more conclusively demonstrated

### *Influence of Hormones on Renal Function*

Facts on the precise individual and correlated influence of hormones on renal function are only beginning to be accumulated. Thyroid extract has a diuretic action on normal subjects usually through its influence on general metabolic processes rather than by control of renal function, although its antagonism to the antidiuretic pituitary hormone has been suggested. The antidiuretic effect of posterior pituitary extract (pitressin) in patients with diabetes insipidus, whose urinary output may exceed 20 liters per day following damage to the posterior lobe, is well known. Small doses of the extract may produce such an antidiuretic effect that it is thought that the action may be due not to vasoconstriction but to action on the epithelium of the renal tubules. The growth hormone of the anterior pituitary gland markedly improves the renal function (PAH and inulin clearances) that had been previously depressed in hypophysectomized dogs (White et al.).

The role of the adrenal cortex in controlling the excretion of sodium and potassium is also recognized as is that of the parathyroid glands in the renal regulation of the levels of phosphates and calcium, and the elimination of water. Polyuria is a common symptom of hyperparathyroidism. However, it is the integrated role of the hormones in the "general adaptation syndrome" that has commanded recent interest. It appears to have been shown by Selye that the administration of adrenocorticotrophic hormone (ACTH) or desoxycorticos-

terone acetate (DCA), especially in animals prepared by unilateral nephrectomy, high sodium diet and certain types of stress (for example, cold) results in the production of lesions of benign and malignant nephrosclerosis, and of periarteritis nodosa. These phenomena may be inhibited by the use of acidifying salts, such as ammonium chloride.

There is no satisfactory evidence that Addison's disease produces any significantly consistent morphologic changes in the kidneys. Whatever impairment of renal function occurs in Addison's disease is secondary to shock, dehydration, and hypervolemia. Between crises, the renal function is not impaired except for some diminution of the rate of glomerular filtration, and some interference with tubular excretion of potassium and reabsorption of water and sodium. These disturbances, which are corrected by specific therapy, present no serious problem except in Addisonian crises.

### *Tubular Reabsorption*

Normally glucose and bicarbonate are reabsorbed completely; sodium, chloride, and calcium are reabsorbed except for a small fraction of 1 to 2 per cent; about 8 per cent of the filtered potassium and about 20 per cent of the uric acid are excreted. The excreted fractions of phosphate and urea are about 45 per cent and 60 per cent, and of creatinine somewhere around 70 per cent.

Much remains to be learned about the role of tubular enzymes in the process of reabsorption and excretion. For example, alkaline phosphatase in the epithelium of the proximal convoluted tubules hydrolyzes organic hexosephosphate with the liberation of glucose to the peritubular capillaries, after preliminary phosphorylation of the glucose. Presumably a similar mechanism for the reabsorption of glucose with the aid of phosphatase obtains in the intestinal tract. In connection with the phosphatases, the early data dealing with the precise types and localization of the phosphatases in various parts of the nephrons to the exclusion of others need to be modified. Standard incubation periods of enzyme and substrate at standard pH may fail to reveal existing phosphatases. Some of the cells, or

some components of cells, require longer incubation than others to demonstrate their content of enzyme by Gomori's method or a modification of it (Gomori, Newman et al.). With such variation in pH and time of incubation, alkaline, as well as acid phosphatase may be demonstrated in both the proximal and distal portions of the nephron; in addition, phosphatases are present in the basement membranes and brush border of the proximal tubules, in the endothelial cells and media of blood vessels, and even in the stromal nuclei. Awareness of the many inhibitors of phosphatase, including cyanide, bile salts, amino acids, heat, and mechanical interferences, is important in the accurate evaluation of this group of enzymes in histologic sections.

### CLEARANCE

The term *clearance* was originally used in 1928 by Møller, McIntosh and Van Slyke to refer to the volume of blood cleared of urea by one minute's excretion of urine. This volume is equal to  $\frac{U}{P}V$ , where  $U$  and  $P$  equal the concentration of urea in the urine and plasma respectively, and  $V$  equals the cubic centimeters of urine excreted per minute. Since then, clearance studies have been applied to a wide range of other substances, including creatinine, diodrast, para-aminohippurate, inulin, phenol red, phosphate, sulfate, amino acids, penicillin, aureomycin, and radioisotopes (e.g.,  $Na^{24}$ ). By the use of one or other of these agents, it is said to be possible to measure glomerular filtration rate, filtration fraction, renal blood flow, and maximal tubular function.

Of all the clearance tests, the urea studies are a particularly sensitive index of renal function, and the most dependably revealing from the point of view of clinical application. Urea clearance tests reflect renal insufficiency earlier than other renal function tests. However, no one test is entirely adequate to disclose all components of renal dysfunction. The average maximal urea clearance is about 75 cc per minute (that is, for urinary excretion of more than 2 cc per minute). Most observers state that it is not until the urea clearance is about

40 per cent of normal that the concentration of blood urea as well as of creatinine become elevated. Goldring and Chasis, however, insist that there is a complete linear correlation between the level of azotemia and the degree of urea clearance. They believe that this correlation is often hidden by extrarenal factors, such as protein intake. For this reason, the statement that urea clearance must be reduced to 40 per cent of normal before azotemia occurs, represents a misconception according to them.

### Principles of Clearance Studies

By interpolating the values of glomerular filtration, tubular reabsorption, and tubular excretion of certain substances, estimates can be made of several features of renal dynamics. These are (1) the volume of glomerular filtrate per unit of time, or filtration rate, (2) the filtration fraction, (3) the rate of renal blood flow and (4) the maximal tubular function.

With the use of a substance such as inulin, clearance values equal those of the *glomerular filtrate*. This is so because the inulin passes the glomerular filter in the same concentration as it exists in the plasma and is neither reabsorbed nor excreted by the tubules. The inulin clearance is determined by the standard

formula  $\frac{U}{P}V$ . The normal clearance is 120 to 130 cc per minute and, as stated, measures the rate of formation of glomerular filtrate. The normal maximal urea clearance is less (75 cc) because, unlike inulin, a certain amount of urea is returned to the plasma by the mechanism of tubular reabsorption. This figure actually signifies that the amount of urea excreted in the urine in one minute is that contained in 75 cc. of plasma. The formula  $\frac{U}{P}V$  applies for urea clearance when more than 2 cc of urine are excreted per minute; if the amount is under 2 cc the formula is  $\frac{U}{P\sqrt{V}}$ , the normal value of which is 54 cc. This dependence of clearance values on the volume of urine applies to the clearance value of urea, but not to the other substances used. This is so because the amount of tubular reabsorption of water determines the volume of urine ex-

creted, and the amount of urea that diffuses back through the tubules is dependent on its concentration in the tubular lumen. This is not the case with inulin, diodrast and other commonly used agents.

There are additional substances which not only are filtered through the glomeruli but are also excreted by the tubules. Phenol red, phenolsulfonphthalein, para-aminoluppuric acid and diodrast are examples of such substances. Diodrast undergoes complete clearance from the blood during one circulation through the kidney. Hence the diodrast clearance is a measure of renal blood flow. The maximal capacity of the tubules to excrete diodrast when the plasma is saturated with this, or a similarly behaving substance is regarded as an index of the total functioning tubular mass (Tm). The Tm would, of course, differ for each substance used.

As would be anticipated, the normal plasma clearance of substances such as creatinine (175 cc), phenol red (400 cc) and diodrast (697 cc) is greater than the clearance of urea (75 cc) and inulin (125 cc). The reason is that to the amount of creatinine, phenol red, and diodrast filtered through the glomeruli, there is added an additional increment to the filtrate by the process of tubular excretion. No tubular excretion of urea or inulin occurs, on the contrary, some tubular reabsorption (about 40 to 50 per cent—Herrin) of urea takes place so that its clearance is less than that of unresorbed inulin. By the same mechanism, it could be guessed that the clearance of glucose at normal plasma concentrations is zero inasmuch as at such levels glucose is completely reabsorbed and returned to the plasma. However, by increasing the concentration of glucose to high levels, the tubular capacity to reabsorb this substance is saturated, so that at such times, the excess glucose in the glomerular filtrate is excreted and the glucose clearance then equals the inulin clearance. This phenomenon of tubular saturation may occur for other substances, for example, it may occur for hemoglobin when the tubular epithelium becomes packed with it or hemosiderin, as in paroxysmal hemoglobinuria (plate 124). The clearance value of glucose when the reabsorptive capacity of the

tubules is saturated is a measure of the maximal rate of tubular reabsorption (for glucose). The value is called glucose Tm and is 320 mg per minute when the plasma level of glucose has been raised from 200 to 800 mg per cent.

A similar process of thought has been applied to the maximal excretion of diodrast and other substances similarly excreted by the tubules, for example, creatinine and phenol red. For these substances there is a maximal quantity which can be handled by the cells of the tubules per unit of time. Therefore, when the plasma concentration is raised above a critical level, the tubular excretory mechanism is fully taxed and the substance is excreted at a maximal rate. This value for diodrast, for example, is the diodrast Tm and is presumed to measure the total quantity of tubular excretory tissue. This tissue is assumed to be the total quantity of intact proximal tubules inasmuch as these are the tubules which are thought to excrete diodrast (as well as creatinine and phenol red). The ratio  $\frac{\text{inulin clearance}}{\text{diodrast clearance}}$  is equal to  $\frac{\text{filtration rate}}{\text{renal plasma flow}}$ . This ratio is equal to the fraction of plasma filtered through the glomeruli and hence is called the filtration fraction (F.F.).

### Limitations of Clearance Studies

It is apparent that many of the determinations of the renal functions of even normal subjects (table 2) are characterized by an impressively wide variability. This deviation from the mean is hardly any less striking in statistical samples of clearance studies (e.g., Earle) purporting to show the pattern of renal functions of diseased kidneys (table 3). It should be mentioned that even when the standard deviation or probable error is indicated on infrequent occasions, the further logical step of calculation of the statistical significance of the mean's from these data (chi square test, for example) is rarely carried out. This is a basic computation that might well dampen the definiteness of many of the conclusions. However, an impression of the extent of the variations is acquired from the data on 7 patients in the nephrotic stage of chronic glomerulonephritis with filtration rates vary-

ng from 11 to 73 per cent of normal (Earle). In 14 patients with acute glomerulonephritis, the filtration rate averaged 55 per cent of normal with a range of 25 to 92 per cent, while the tubular mass averaged 70 per cent of

course been aware of many of the limitations Smith (1941) anticipated criticism of the use of these methods for the interpretation of the physiologic and morphologic status, particularly of diseased kidneys. He acknowl-

TABLE 2 — Mean Values for Renal Function in Normal Subjects (According to Goldring and Chasis)

	Males	Females
Rate of glomerular filtration ( $C_{In}$ , inulin clearance, cc/min)	131 ± 21.5	117 ± 15.6
Effective renal plasma flow ( $C_D$ , diodrast clearance, cc/min)	607 ± 135.9	504 ± 102.4
Maximal tubular excretory capacity ( $Tm_D$ , diodrast $Tm$ , mg iodine/min)	51.8 ± 8.73	42.6 ± 9.46
Maximal tubular resorptive capacity ( $Tm_G$ , glucose $Tm$ , mg glucose/min.)	375 ± 79.7	301 ± 55.3
Filtration fraction ( $\frac{C_{In}}{C_D}$ ) %	19 ± 0.02	20 ± 0.03
Effective renal plasma flow $\frac{C_D}{C_{In}}$	14.0 ± 2.16	14.2 ± 2.30
Maximal tubular excretory capacity $Tm_D$	2.63 ± 0.31	2.81 ± 0.50
Rate of glomerular filtration $\frac{C_{In}}{C_D}$		
Maximal tubular excretory capacity $Tm_D$		

TABLE 3 — Values for Renal Functions in Subjects with Abnormal Kidneys (Earle<sup>4</sup>)

Renal functions in nephrotic edema

	FE <sup>2</sup>	SE <sup>2</sup>	SN <sup>2</sup>		GR <sup>2</sup>	NT <sup>2</sup>
	"Nephrotic glomerulonephritis"	Amploudous	"Nephrosis"	Healed 5 yrs. later	Heart failure	Acute glomerulonephritis
Filtration rate, cc/min (F R)	25	45	125	122	54	33
Renal plasma flow, cc/min (R P F)	173	397	708	679	137	458
Filtration fraction, % (F F)	14	11	15	18	39	7
$Tm$ P A II, mg/min	14	20	96	90	—	31
$Tm$ glucose, mg/min ( $Tm_G$ )	179	—	—	—	—	—
Urea clearance, % normal	—	—	145	—	64	29
	Essential Hypertension <sup>2</sup>	Lupus Erythematosus <sup>2</sup>	Diabetic Glomeruloclerous <sup>2</sup>		Chronic Glomerulonephritis <sup>2</sup>	
F R	60	42	40		45	
R P F	277	695	199		262	
F F	22	8	20		17	
$Tm$ P A II	38	—	32		44	
$Tm$ glucose	—	262	131		—	
Urea clearance	—	—	—		90	

normal with a range of 36 to 125 per cent. At least one of his patients with a "definite chronic nephritis" had a normal functional pattern as revealed by clearance studies. Such variation is further emphasized by contrasting the data on similar conditions originating in other leading laboratories.

Those engaged in clearance studies have of

edged that the glomerular permeability to inulin may be diminished without proportionally retarding the filtration of water, and that diseased tubules might allow water to escape to the exclusion of inulin, without in either case, having the differential changes detected. The observation that similar clearance values can be obtained by the use of a



substance with a molecule smaller than that of inulin only partially reduces this limitation. After all, to find, as Raaschow has, that inulin clearance may be markedly reduced in pyelonephritis, with histologically intact glomeruli, or that the urea clearance may be markedly reduced with infections and jaundice in the presence of histologically normal glomeruli (Hayman et al.), or that there are significant discrepancies between the renal blood flow calculated by clearance tests and that measured directly (Selkurt), raises some doubt as to the validity of the use of these methods as a measure of glomerular filtration in diseased kidneys or in diseased states.

The recorded frequency of such discrepancies is less important than the fact that the neat correlation between physiologic and morphologic data can be completely disrupted for the reason that function has been altered by structural change in ways that need to be known, but obviously are not. The glomerular filtrate of some nephrons may never reach the collecting tubules because it has escaped into the interstitial fluid or has been otherwise diverted. Such losses distort the clearance values. And yet, it is just this mode of loss of filtrate that, on the one hand, has been postulated as occurring in hemoglobinuria (lower nephron) nephrosis, and, on the other, is found to be awkward and hence is disregarded in drawing conclusions (Earle\*) from the clearance studies.

In addition, all would agree with Smith that the presence of inert tissue should not distort the ratio  $C_D/TmD$ . However, if the tissue is not quite inert, but is functional in varying degrees as a result of renal structural disease, can it properly be assumed that the altered tubules reabsorb and excrete in the qualitative manner of normal tubules? It is wisely noted (Shannon, 1939) that from the standpoint of comparative physiology, the mechanisms for tubular excretion become more important in those species characterized by poor glomerular development, becoming paramount in those that are completely aglomerular. Is it therefore not entirely reasonable to suggest that with conspicuous changes in glomerular as well as tubular structure, the

test substances may be handled by glomeruli, tubules and capillaries in a manner different from that in which they are handled normally?

Furthermore, the value for maximal tubular function ( $Tm$ ) is said "under ordinary circumstances" to be independent of changes in glomerular filtration rate (Earle\*). Nevertheless, as Earle points out, "the large and acute variations (caused by administration of fluid) during the procedure render interpretation of the relationships quite unsatisfactory at times." It is appreciated also that there may be difficulties in achieving saturation of blood for the measurement of  $Tm$ 's in the presence of greatly reduced values of filtration rate and renal plasma flow, especially when tubular function has not been seriously impaired. There is the additional possibility that the administration of large amounts of material for measuring  $Tm$ 's may cause renal vasoconstriction. Moreover, it is a recognized fact that diminished capacity of the tubule to concentrate urine and to form ammonia may occur without reflection of that impairment in the values of  $TmPAH$  or in  $Tm$  glucose.

When the renal extraction ratio is low, there is admittedly great danger of reaching erroneous conclusions in the study of most renal diseases (Earle\*, 1930). [This ratio is determined with the use of blood collected from the renal vein by catheterization (Warren et al.)] It is known that low renal extraction ratios of clearance substances occur in cases of advanced renal diseases, for example, benign nephrosclerosis and chronic glomerulonephritis (Bradley et al., Cargill). Clearly, this represents a serious limitation to the method and invalidates many of the findings of past investigations by clearance studies and perhaps helps to explain many of the contradictions.

While acknowledging the resourcefulness of the investigators of the clearance studies, we must avoid the error of using an exact measurement to define the limits of function of a structure, when that datum represents merely an algebraic composite of various degrees of functions of structures in various states of morphologic preservation. As Oliver forcefully

emphasizes (1930), such a composite may include many basically different functional and morphologic components, more or less individually modified by pathologic processes. It appears to be a practical fact that technically advanced clearance studies generally offer no greater practical revelation concerning prognosis and diagnosis of renal disease than can be learned by simpler tests. The clearance tests, after all, are not measures merely of renal function but of many ancillary functions related to water, electrolyte and hormonal balance, through which the entire body influences the excretion of urine. As others have pointed out, if these extrarenal functions are assumed to be quite normal, then the clearance tests may be considered measurements strictly of renal function. The fact is that such an assumption is often not warranted clinically. As one example, in congestive heart failure, the glomerular filtration rate is about two-thirds of normal (66.8 cc/min) and the renal plasma flow is approximately one-third of normal (191.5 cc/min). Inasmuch as myocardial failure of some degree occurs in many renal diseases including even acute diffuse glomerulonephritis (LaDue), it is obvious that the extrarenal factors can influence appreciably the figures of renal clearance, and, therefore, deflect accurate interpretation of the structural disorders of the kidneys. To paraphrase Addis, it is not enough to know what the kidney is doing in terms of arithmetical summations of functions; for diagnostic, prognostic and therapeutic reasons it is essential to know the component factors that are at fault.

In summary, the limitations of the more elaborate clearance tests on the kidneys with appreciable structural damage are imposed by the several conditions mentioned, as well as by the fact that the physiologic influences of such organic damage are often not in the same cumulative direction. In other words, abnormal function may be camouflaged by an algebraic summation of two or more disturbed physiologic processes, for example, glomerular, tubular and prerenal, so that the final measurement of the derangement may be even a normal value.

In normal subjects, it is theoretically possible that the functions of individual renal components may indeed be estimated with these astutely contrived clearance tests. Even in such instances, the variability of the results is considerable. However, in kidneys with characteristically variegated morphologic damage, not only from one nephron to the next, but even within a small segment of a nephron, the determination of filtration rates, filtration fractions, effective renal blood flow, and tubular excretory and secretory capacity—no matter how meticulously performed—are fraught with masked, obscurely neutralizing, as well as additive renal activities. By no phrase is it meant that this method of study of renal function is without considerable use, it should be stressed, however, that interpretations of the tests on structurally damaged kidneys have often been unjustified and without adequate regard for the correlative morphologic changes. Undoubtedly, future integrative refinements of method will reduce the limitations of the tests. In the meantime, there is nothing to be gained by a blanket subordination of histologic data to arbitrary structural inferences based on the clearance studies.

#### RENAL FUNCTION IN INFANTS

As McCance has aptly demonstrated, the differences in renal function in the newborn and in adults are of a quantitative rather than qualitative nature. There is a reduction in the clearance of most test substances, especially of those that are cleared by glomerular filtration. The urine of the infant, and more particularly of the fetus, is less concentrated than that of the adult. Possibly these features are dependent on the incomplete development of the loops of Henle, and on the prominent visceral epithelial cells of the glomerular tuft serving as a barrier to filtration. In addition, the subcapsular glomeruli are usually immature at term (plate 5 B). At any rate, the practical point is that the functional flexibility of the kidneys of the newborn is limited, and their adaptability to acidosis, dehydration, surgical procedures, and other stresses is correspondingly limited. This type of narrow

reserve in infants is, of course, not unique with the kidneys, but is common to other organs

### CASTS

Casts are visible in histologic sections of the kidney as well as in the urine. The casts are classified as: (1) hyaline, (2) epithelial, (3) granular, (4) waxy, (5) cylindroids, (6) broad renal failure casts, (7) blood casts, (8) bile casts, (9) melanin casts, (10) calcium casts, (11) uric acid casts. Casts are rarely found in the proximal portion of the nephron, they begin to form at the level of the distal convoluted tubules. The reasons for this are, first, that the glomerular filtrate is almost always insufficiently concentrated to form casts until it reaches the distal nephron. Secondly, the rate of flow of the glomerular filtrate is about 100 times greater than that in the collecting tubules (Addis) and is therefore too rapid for the accumulation of casts. Undoubtedly additional factors, such as oliguria, pH, and isoelectric point play a role in their formation. Casts tend to disintegrate in the urine so that examination for them should be made with recently passed samples. This is particularly true of urine that is alkaline when passed or that is made alkaline by the bacterial decomposition of urea with the resultant formation of ammonia.

#### *Hyaline Casts*

Hyaline casts are gels soluble in water (Addis) and in dilute acetic acid, formed by a combination of protein and sulfur-containing polysaccharide. Chemical analysis of hyaline casts (Addis) reveals them to be composed of

C	= 48.6%
H	= 2.4%
N	= 11.3%
S	= 2.6%

length and 10 to 50 microns in thickness. Often granular fragments of epithelium, fat droplets, and blood are admixed with the sticky hyaline cast. Occasional hyaline casts may be incidental findings in sections of kidneys or they may be numerous as in renal

amyloidosis (plate 25 E). As a rule, these casts provoke no tubular reaction, although postmortem desquamation of epithelium may simulate degenerative change. In some instances of renal reaction to sulfonamides, these casts are associated with prominent giant cell granulomas and thrombophlebitis of adjacent interlobular or arcuate veins (plate 143, 144A). In sections of myeloma nephrosis, the casts are accompanied by a characteristic syncytium of tubular cells (giant cells) (plate 150). The damage wrought or reflected by hyaline casts, as with other types of casts, is to be judged in sections by their number and density; their presence in isolated foci in sections, or in small numbers in the urine, is not clinically meaningful. Hyaline casts may be found in large numbers in the urine in most instances of albuminuria. They may be present in large numbers in cases of chronic passive congestion, during recovery from acute glomerulonephritis even after albuminuria has disappeared, prior to the onset of diabetic coma, and in cases of jaundice (Fishberg).

#### *Epithelial Casts*

Cylindroids resemble hyaline casts qualitatively, but are longer and taper to a point at either end. They are found in more or less the same conditions as are hyaline casts. Because cylindroids may be found in the urine associated with inflammatory conditions of the urinary tract distal to the kidney, it is thought some cylindroids may not originate in the kidney but represent mucoid products of inflammation. The epithelial casts are formed from desquamated tubular epithelial cells or granular fragments of them. Epithelial casts may be combined with hyaline casts. The fragments may contain lipid hemosiderin, bile or melanin and thereby furnish clinically important information. For example, hemosiderin granules are suggestive of abundant hemolysis as in nocturnal hemoglobinuric nephrosis, the lipid granules, especially if birefringent, are indicative of the nephrotic syndrome or of the several other conditions in which the tubular epithelium may be laden with fat, e.g., diabetes mellitus, phosphorus or carbon tetrachloride poisoning (plate 66 C,

TABLE 4—Normal Values of Relative Concentration of Substances in Urine and Blood (Fishberg)

	Concentration in urine mg %	Concentration in blood mg %	Concentration ratio	Concentration in blood in renal insuffic
Urea	2000	30	66.6	Increased
Uric acid	60	2	30	Increased
Creatinine	75	2	37.5	Increased
Indican	1	0.05	20	Increased
Phosphate	150	3	50	Increased
Sulfate	150	3	50	Increased
Potassium	150	20	7.5	Slight increase
Chloride	500	350	1.4	No increase
Sodium	350	335	1	No increase
Calcium	12	10	1.5	No increase

75, 107) Addis believed that the *granular* and *waxy* casts were progressive stages of autolytic transformation of the epithelial casts. The waxy cast (which, of course, has no reference to the waxy or amyloid kidney) forms after prolonged stasis (anuria) in a given nephron. The autolysis of the epithelial cast may occur in the urine within the bladder (Addis). Of particular interest are the *broad renal failure casts* (plate 71). These are epithelial, granular or waxy casts which have stagnated in the collecting tubules and ducts of Bellini and, in large numbers, they are indicative of severe oliguria or anuria when observed in histologic sections.

#### Pigment Casts

Pigment casts are currently the source of much discussion and speculation, particularly with regard to their functional significance. The casts of hemoglobin and myoglobin—and often the casts of bile—are indistinguishable by routine methods of staining paraffin or frozen sections of tissue. Spectroscopic methods may soon be applicable to their differentiation in sections. The benzidine-hydrogen peroxide stains are unreliable in their identification of hemoglobin versus bile. Hemoglobin casts resulting from laking of red blood cells already within the tubular lumens must be distinguished from hemoglobin casts produced by hemoglobinemia. The casts themselves may look alike, although in the case of hematuria, some intact red blood cells may be included within the casts (plate 130). Contrary to standard impressions obtained from the literature, the tubular epithelium about casts of hemoglobin may be—and usually is—histo-

logically intact (plate 128, 130). Isolated hemoglobin casts are commonly present in a loop of the distal convoluted tubule in the vicinity of the glomeruli in many conditions, especially in infectious diseases. In hemoglobinuric nephrosis, these casts are predominant in the collecting tubules of the medulla (plate 128).

Bile casts are often greener than hemoglobin casts but may look alike in routine paraffin sections stained with hematoxylin and eosin. The tubular epithelial reaction to bile is similar to that of other pigments including hemoglobin, myoglobin and melanin (plate 133, 134, 328). The bile casts are located similarly to the hemoglobin casts. Renal casts of melanin are pathognomonic of the existence of malignant melanoma. They are found in the distal tubules (plate 125) and are of no renal functional significance.

Calcium casts are formed by agglutinated concretions of desquamated, calcium encrusted epithelium, in practically all instances from the distal tubules. These casts occur in association with alkalosis, lesions of bone, hyperparathyroidism, and idiopathic hypercalcemia. They are usually of little consequence, unless they occur in critical locations, as in the apex of the pyramids where they may exert serious obstructive effects (plate 197).

Uric acid, or urate casts, are composed of crystals formed physiologically in the newborn, in gout or in leukemia following therapeutic destruction of nuclear material. They do not compromise renal function except in certain instances of gout (plates 151, 155). Further discussion of the casts is included in the sections dealing with the individual diseases.

TABLE II—Normal Volume of Urine (Kolmer and Boerner)

Age	cc per 24 hours
1 to 2 days	15 to 60
3 to 10 days	100 to 300
10 days to 2 months	250 to 450
2 months to 1 year	400 to 500
1 to 3 years	500 to 600
4 to 10 years	600 to 1000
9 to 15 years	800 to 1400
Over 15 years	1000 to 1600

TABLE III—Normal Constituents of Urine (Grams per 24 hours)

Total solids	60-70 Gm
Titrateable acidity	200-500 cc N/10 alkali
Potassium (as $K_2O$ )	2.0-2.5 Gm
Calcium	0.1-0.3 Gm
Total sulfur (as $SO_2$ )	1.5-2 Gm
Magnesium (as $MgO$ )	0.2 Gm
Chloride (as $NaCl$ )	5-15 Gm
Phosphorus	2-4 Gm
Sodium (as $Na_2O$ )	4.0-4.5 Gm.
Iron	0.003 Gm
Reducing substances	0.5-1.5 Gm
Total nitrogen	8-18 Gm
Urea	12-30 Gm
Amino acids	0.1-0.15 Gm.
Ammonia	0.6 Gm
Uric Acid	0.4-0.7 Gm
Creatinine	1.5 Gm
Urobilinogen	1-5 Ehrlich units
Gonadotropin	
Men	26-105 mouse units
Women	13-105 mouse units
17-ketosteroid excretion	
Men	7-14 mg
Women	4-11 mg
Children	<1 mg

Traces of the following organic substances are also present

pigments, sugar (2-3 mg per cent), fatty acids, carbonates, diastase, and mucinous compounds

#### SUMMARY OF REPRESENTATIVE RENAL FUNCTION TESTS

##### Phenolsulfonphthalein Test

Intravenous	Intramuscular
First 15 minutes 25-50%	First hour 40-60%
Second 15 minutes 15-25%	Second hour 20-25%
Average total in 30 minutes 50%	Total 60-85%
Second 30 minutes 10-15%	
Total, 60 minutes 60-65%	
120 minutes 70%	

The appearance of the dye may be delayed by ether or any deep anesthesia. Advantages in fractionation of the data are conceded.

##### Urea Clearance

Maximal: 75 cc. of plasma cleared per minute (100%).

Standard: 54 cc. of plasma cleared per minute (100%).

##### Inulin Clearance

120-130 cc of plasma cleared per minute.

##### Creatinine Clearance

175 cc. of plasma cleared per minute

##### Diodrast Clearance

700 cc of plasma cleared per minute.

##### Fishberg's Concentration Test

In at least one specimen the specific gravity is greater than 1.022 and often reaches 1.032

##### Fishberg's Dilution Test

1200 cc. of water drunk within 4 hour are normally eliminated in less than 3 hours and the specific gravity of the largest specimen is about 1.002.

##### Volhard's Dilution-Concentration Test

About 1500 cc of urine are excreted within 4 hours after 1500 cc of fluid are drunk. The specific gravity is lowered to 1.002. After withholding fluids, the specific gravity normally rises to about 1.030.

##### Concentration Tests of Addison and Shelly

The specific gravity of the urine reaches 1.026 to 1.032 after abstinence from fluids for 24 hours.

[Note: Several substances in the urine may elevate the specific gravity without reflecting the ability of the kidney to concentrate. Diodrast, albumin

(Albarran) ]

The normal range of the specific gravity of the urine spans at least 0.010. The volume of urine formed in the 12 hour night period is about 400 cc., with a specific gravity of approximately 1.018. The volume of the 12 hour day period is about two to three times as great. Factors such as fluid intake, weather, exercise, etc., obviously modify these values. The capacity to concentrate the urine is indicated by the terms, originally suggested by von Kórányi, hypersthenuria, isosthenuria, and

hyposthenuria. The designation "hyposthenuria" was based on the determinations of freezing points of the urine. Inasmuch as the freezing point is an indication of the number of particles in solution, it is more or less a measure of the specific gravity, notwithstanding the fact that large protein molecules may have a disproportionately greater effect on the specific gravity than on the freezing point. Hence, these terms are now used to indicate the range of specific gravity of the urine. In hyposthenuria the patient is unable to concentrate the urine and its specific gravity remains below 1.010, while the freezing point, incidentally, is close to that of blood, i.e.,  $-0.56^{\circ}\text{C}$ . In patients with isosthenuria, the specific gravity of the urine stays at 1.010, which is the specific gravity of the glomerular filtrate, or plasma minus the proteins. In renal disease, both hyposthenuria and isosthenuria are evidences of the inability of the kidney to concentrate urine, and therefore of severe impairment. The low specific gravity of the urine in diabetes insipidus, for example, is another matter altogether, since the urine of such patients can be made more concentrated with extract of posterior pituitary gland.

# ADDIS COUNT

The Addis Count refers to the elements concentrated in the urinary sediment excreted during a 24-hour period, during which the patient has taken no fluid. The sediment is examined unstained in a blood counting chamber and separate counts are made of (1) the red blood cells, (2) epithelial and white blood cells combined and (3) the casts. The average counts of these elements for a normal person per 24-hour period are:

- (1) Red blood cells, 130,000
- (2) Epithelial and white blood cells, 650,000
- (3) Casts, 2,000
- (4) Protein: 10 mg

These counts are modified by exercise and various pathologic states. The general attitude toward this procedure is that it is useful in investigative studies but not practical as a routine method. Hence, it has not achieved widespread use. Certainly, Addis, his associates, and others have made interesting, informative, and practical use of the method which is not nearly as complicated, nor as time-consuming, as it is commonly thought to be.

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## 4. Uremia

### DEFINITION

UREMIA ("urine in the blood") represents a symptom complex resulting from renal insufficiency due either to an organic or merely functional disorder of the kidney. Within the scope of this definition is included "prerenal" uremia in which renal function is compromised because of an extrarenal disorder of circulation or homeostasis, such as protracted vomiting or diarrhea, diabetic coma, Addison's disease, shock of various types and intestinal obstruction.

### RENAL CAUSES OF UREMIA

Any disease of the kidney may result in uremia if a sufficiently large portion of the organ becomes functionally incapacitated. The amount of intact kidney that is required to keep it functionally solvent depends on the rapidity with which the remainder is destroyed, and on the counterbalance of the opposite kidney. This is very much the situation that is found in other organs, such as the adrenal glands, or when there is loss of blood. Obviously a much greater degree of blood destruction may be survived if the loss occurs over a long period of time as against a sudden massive hemorrhage. It is the same with the kidneys. In chronic renal disease, more than three fourths of the parenchyma may be destroyed before the renal function is reduced to the uremic level.

More specifically, uremia occurs in acute interstitial nephritis, in acute, subacute, and chronic glomerulonephritis, in eclampsia, and in disseminated lupus erythematosus, occasionally in focal endocarditic glomerulonephritis. It occurs usually in the fatal cases of the necrotizing nephroses, such as those due to mercury bichloride, diethylene glycol, potassium chlorate and chromate, and other agents. Uremia may complicate hemoglobinuria (lower nephron), cholemic, and ethylene glycol nephrosis. Bilateral cortical necrosis, massive infarcts, malignant (accelerated) nephroscler-

osis, and polycystic kidneys may be associated with uremia, as may suppurative pyelonephritis, renal amyloidosis, periarteritis nodosa, diabetic glomerulosclerosis, and, of course, any other diseases associated with excessive destruction of renal tissue. Only about 7 per cent of the cases of benign arteriolar nephrosclerosis (of essential hypertension) terminate in uremia.

### CLINICAL PICTURE OF UREMIA

Uremia is a clinical complex of symptoms that usually, although not always, begins insidiously, generally lagging behind the onset of renal insufficiency. This latent period may vary from several days to a week and in special instances, as in cases of polycystic kidneys, azotemia may be present over a year before symptoms of uremia appear. The uremic signs and symptoms may involve, in addition to the kidneys, (1) the nervous system, (2) the alimentary tract, (3) the respiratory tract, (4) the circulatory system, (5) the skin and (6) miscellaneous organs.

#### *The Nervous System*

The nervous signs and symptoms include dull headaches, vertigo, muscular weakness and twitchings, apathy, inability to concentrate, restlessness, neuralgic pains, thick speech, drowsiness or insomnia, transitory or constant disorientation and delirium. The reflexes may be exaggerated in uremia but abnormal reflexes do not occur except as a result of complications such as encephalomalacia or hemorrhage. The lowered level of calcium may be responsible for the lively reflexes as well as for the fairly common Chvostek sign. Tetanic manifestations may be initiated also by the acidosis or by alkalosis due to excessive use of alkali, to vomiting, or to a reorientation.

#### *The Alimentary Tract*

The involvement of the alimentary tract manifests itself by dryness of the mouth

the tongue coated brown or grey, uremic ulcerative stomatitis, purpura and loosening of the teeth. The stomatitis may cause a particularly offensive, fetid odor of the breath. Anorexia, polydipsia, nausea and vomiting may be the initial uremic symptoms and may be mistaken for an intrinsic gastric disorder. Meat may be particularly distasteful. The vomiting, or retching, may be continuous and, at times, projectile, it is thought to be of central origin. Fishberg suggests that, in view of the high nonprotein nitrogen content of the gastric juice, the vomiting may serve as a means of vicarious excretion, and, to be sure, one of the current modes of therapy of uremia consists in repeated gastric washings to eliminate the retention products.

Constipation may be present at the onset of uremia, but on the other hand, severe diarrhea may be the outstanding symptom of uremia and may be accompanied by tenesmus, cramps and bloody stools. The diarrhea, too, may serve to rid the body of waste products. The corresponding therapeutic procedure is to wash the gut with dialyzing solution either by means of a two-way tubal system or by surgically isolating a segment of bowel.

### *Respiratory System*

One of the characteristic clinical signs of uremia is the typical uremic odor to the breath. The odor is ammoniacal and is believed to be due to the production of ammonia from bacterial decomposition of the abnormally large amount of urea in the saliva. Kussmaul breathing, as a result of acidosis, occurs in the late stages. The breath sounds are said to be unusually dry and harsh. An interstitial pneumonia occurs frequently in uremia.

### *Circulatory System*

Hypertension is commonly associated with uremia but this association is due to the underlying renal disease rather than to the uremia. All patients in uremia are not hypertensive. The cardiac failure which may occur in uremia is, in most instances, due to coronary insufficiency, or to myocarditis secondary to infection.

Sterile, serofibrinous pericarditis is a common terminal feature of uremia particularly in

cases of chronic renal disease. The precise cause of the pericarditis is not known although it is believed to be due to one or more of the retention products. Certainly there is no correlation between the level of any one of the retention products and the development of pericarditis.

In recent years, the role of an elevated level of potassium has been given increasing emphasis in the cardiac failure of uremia. Hyperkalemia is common in uremia and may be associated with a characteristic electrocardiographic picture and occasionally with focal myocardial necrosis (plate 28 B). These features are discussed in a subsequent paragraph.

### *Skin*

The skin in uremia is generally dry, waxy, yellowish-brown and pruritic. The yellow color is thought to be due to pigmentation by retained urochromes. The "uremic frost" is not a common phenomenon, when it does occur it signifies impending death. The "frost" is due to the deposition of greyish-white urea crystals, mostly on the face, neck and chest (plate 26). Other uremic eruptions include purpuric, erythematous, eczematoid, lichenoid, papular and vesicular rashes. Patients in uremia appear also to have an increased susceptibility to drug eruptions.

### *Miscellaneous Manifestations*

The temperature in uremic patients is often subnormal but unusual instances of hyperpyrexia are recorded. Emaciation, at times masked by edema, is common in uremia. Diphtheritic and hemorrhagic ulcerative colpitis may occur. Anemia is the rule and may be of severe degree as well as rapid in development. The characteristics are those of a secondary anemia but the mechanism of its production is not clear. In general, however, depression of the bone marrow is favored over hemolysis as the basis for the anemia. A hemorrhagic diathesis is common in uremia. The coagulation time is usually increased.

### *PATHOGENESIS OF UREMIA*

Most of the retention products have been individually held responsible at one time or



FIG. A Uremic frost in a 32 year old patient in the terminal stage of chronic glomerulonephritis. The whitish specks of urea crystals are seen especially well near the inner canthus of the eye.

FIG. B Uremic frost. Sections of skin from patient illustrated in figure A. Xanthidrol urea crystals in epidermis and keratotic follicle. The tissue was treated with xanthidrol.

FIG. C Xanthidrol-urea crystals in a sebaceous gland from patient in figure A.

another for the syndrome and the pathologic changes of uremia. Urea, phosphates, creatinine, guanidine, magnesium, potassium, phenols, aromatic oxyacids and other compounds have been regarded as the basis for the toxicity. In addition, such factors as alterations in osmotic pressure of the blood, dehydration, and salt depletion have been thought to play significant roles. In a condition where many kinds of changes occur in the levels of the constituents of the blood, the unitary pathogenetic theories would seem inadequate. It appears more likely that the clinical and pathologic picture may be the resultant of the effect of several of the abnormally accumulated or depleted products rather than of a specific uremic toxin. The problem is not resolved by the experimental administration of the individual retention products and the clinical observation of their effects. It is entirely possible that substances that are by themselves innocuous or severely toxic may behave quite differently in their synergistic relationship with other compounds.

#### LABORATORY DIAGNOSIS OF UREMIA

In addition to the signs and symptoms previously listed, certain laboratory data reinforce the diagnosis of uremia. Elevation of blood nonprotein nitrogen and the occurrence of oliguria with low specific gravity of urine is adequate evidence for practical purposes. A normal quantity of urine may be excreted when there is extreme renal impairment associated with a maximum specific gravity of 1.010. The mere presence of azotemia is not proof that the symptoms in a given case are due to uremia. That is to say, azotemia is of course not synonymous with uremia. In such instances of prerenal azotemia, a specific gravity above 1.020 in the absence of oliguria demonstrates as does a normal excretion of phenolsulfonephthalein, that the kidneys are not primarily responsible for the azotemia.

In general, a determination of the blood urea nitrogen is preferred to that of nonprotein nitrogen, because urea is a specific individual substance, whereas nonprotein nitrogen represents a variety of substances [urea, creatine, creatinine, uric acid, ammonia, amino acids,

and "undetermined nitrogen" (polypeptides, histones)] which may be influenced by extraneous factors. Moreover, inasmuch as urea clearance is a popular investigative procedure in which blood urea nitrogen determinations are also required, there is generally little point to supplementary determinations of the nonprotein nitrogen. However, under certain conditions, knowledge of the blood levels of both urea nitrogen and total nonprotein nitrogen is informative. This is particularly true in cases of acute severe hepatic damage in which the failure of the liver to deaminate the amino acids results in low blood concentrations of urea. This decreased level of urea nitrogen, which is noted also in eclampsia, may be deceptive from the point of view of renal function. Conversely, the nonprotein nitrogen in cases of acute, widespread, hepatic damage may be abnormally high because of the contribution by the unduly high amino acid fraction. In other words, in the presence of extensive acute hepatitis, the evaluation of renal insufficiency must be made with an awareness that the liver itself is a factor on the one hand, in the elevation of the nonprotein nitrogen and on the other, in the diminution of the level of blood urea nitrogen by failing to release its precursor (amino group) from the amino acids. The ratio of blood urea nitrogen to amino acid nitrogen is normally 2 to 1; in acute necrotizing hepatitis, this ratio is decreased.

There is no set level of blood urea nitrogen at which uremic symptoms begin to be noted. Rarely, such symptoms occur when the blood urea nitrogen is less than 100 mg per cent, particularly if the protein content of the diet has been restricted, on the other hand, patients, especially those with polycystic kidneys, may be ambulatory with only minor complaints and with a blood urea nitrogen level over 100 mg. per cent (Fishberg).

The rise in the level of uric acid parallels that of urea nitrogen although occasionally extrarenal factors may influence the hyperuricemia. In normal pregnancy and in eclampsia, for example, the uric acid in the blood may be disproportionately elevated, and the blood urea nitrogen tends to be low. The elevation of the creatinine concentration tends to go

A



B

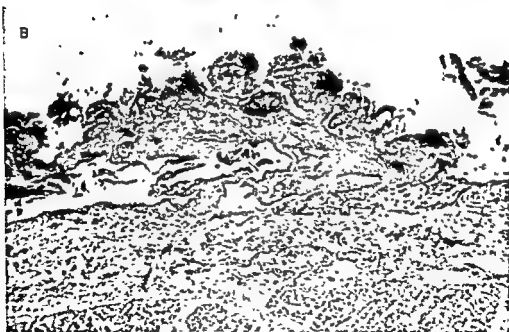


FIG. A Sterile uremic fibrinous pericarditis indistinguishable from a variety of types of pericarditis including rheumatic pericarditis

FIG. B Uremic fibrinous pericarditis corresponding to the sterile pericarditis illustrated in figure A

along with the retention of urea. Again, exceptions occur, as in some cases of acute and chronic glomerulonephritis, in which an appreciable rise in the level of urea nitrogen may precede that of creatinine. The relative disparity of glomerular and tubular damage in many cases of glomerulonephritis possibly accounts for this dissociation of the two metabolites.

As a rule, *chloride* is diminished in the blood in renal insufficiency as a result principally of vomiting, decreased intake of salt, and the shift, stimulated by acidosis, of hydrochloric acid from plasma into the red blood cells. Moreover, in renal failure, chloride may be excreted into the urine despite a low level of blood chlorides. However, in the absence of vomiting, and in some glomerulonephritic patients with edema, the blood chloride level may be elevated, at times to over 1000 mg per cent (as sodium chloride).

*Phosphates, sulfates, and neutral sulfur* are also increased in renal insufficiency, as are indican and other products of intestinal putrefaction, and often the urochromogens. The values for ammonia and magnesium in the blood are not significantly altered, the level of the magnesium may be elevated but slightly (Bradley). Except for those cases with the nephrotic syndrome, or in pregnancy, cholesterol tends to be low in renal failure.

#### *Potassium in Uremia*

Increasing attention is being paid to the elevated levels of serum potassium in acute renal insufficiency. Knowledge of the effects of potassium is one step in the resolution of the problem of the mechanism of uremic intoxication. It is now clear that the precipitating cause of death in many cases of uremia is the cardiotoxic effect of hyperkalemia. Hyperkalemia occurs also in adrenal insufficiency, severe dehydration and shock.

The signs and symptoms of hyperkalemia (normal 3.5 to 5.3 mEq/liter) are primarily cardiovascular, but may also include listlessness and mental confusion, paresthesias, flaccid pareses or paralyses. The cardiovascular manifestations are bradycardia, arrhythmias, poor heart sounds, and peripheral vascular collapse.

The electrocardiographic findings, especially when observed serially, may be strongly suggestive of either hyper- or hypokalemia. With elevated levels of potassium, the first change is in the T-wave which becomes tall and peaked when the serum concentration is from 6.5 to 8 mEq./liter. With higher concentrations, there develop heart block and arrhythmias, wider PR intervals leading to auricular standstill and a biphasic curve with increasing delay in ventricular conduction until cardiac arrest occurs. Focal myocardial necrosis has been attributed to hyperkalemia (plate 28B). Relief of the various signs and symptoms, including reversal of the electrocardiographic changes, follows restoration of the serum potassium to the normal level.

Hypertonic glucose, 10 per cent calcium gluconate, and, above all, restriction of the intake of potassium are of help in combatting potassium intoxication. It is important to bear in mind that, whereas the administration of potassium compounds for therapeutic purposes (as in syphilis, bronchitis, etc.) ordinarily does not carry any significant hazard, there is great danger of potassium retention of therapeutically administered potassium salts in the presence of renal insufficiency. Moreover, potassium intoxication may manifest itself at lower serum levels than would be required in the absence of renal dysfunction. Occasionally, deficiency of potassium may exist in the cells (e.g., of the myocardium) notwithstanding a normal or even elevated level of serum potassium. This paradoxical situation may be noted in severe dehydration, in which, after fluid has been administered, the serum concentration of potassium may fall to low levels (Darrow).

Infrequently, uremia is associated with hypokalemia in which the signs and symptoms are muscular pareses, ileus, and electrocardiographic changes consisting of flattened T-waves, depressed ST segments and prolonged A-V intervals. In addition, hypokalemia has been found experimentally to produce tubular necrosis, lipodosis, calcification and dilatation within the kidney (Foliss et al.).

#### *Sodium Depletion*

Data on the mechanism and serious clinical effects of depletion of sodium or sodium chloride

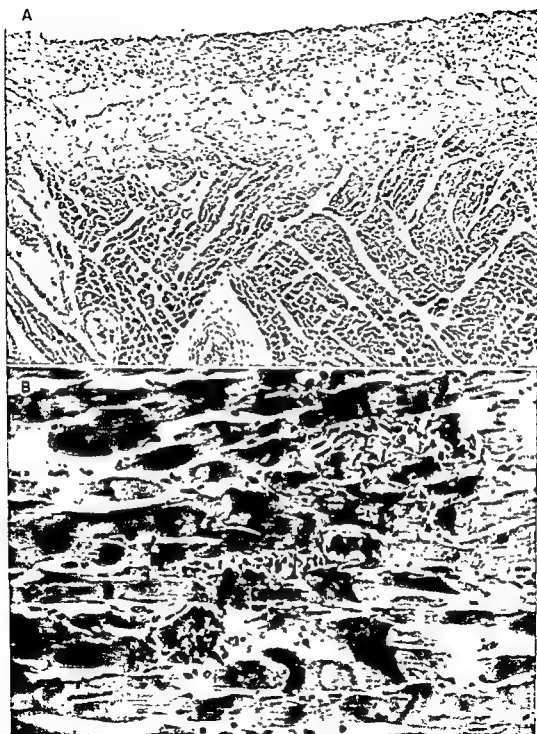


FIG. A *Uremic pericarditis* without fibrin but characterized principally by lymphocytes and histiocytes

FIG. B *Hyperkalemia* with focal myocardial necrosis, these foci of necrosis were numerous



furnish still another increment to our information on the mode of toxicity in uremia. In the past, emphasis has been placed on salt restriction in hypertensive and cardiorenal disease because of the potentiating effect of sodium chloride in these conditions. Clinically, as well as experimentally (Allen, Selye), however, such restriction of salt, especially in association with loss of salt, may be inadvertently overdone.

It has been observed (Poll and Stern, Soloff and Zatarachi, DeGraff and Nadler) that the excessive loss of salt following salt restriction and mercurial diuresis in patients with cardiac or renal edema may lead to fatal complications. The signs and symptoms of the "salt depletion syndrome" include nausea, anorexia, apathy, mental confusion, muscle cramps, vasomotor collapse, azotemia, and reduction in levels of blood sodium and blood chloride. This symptom-complex may be simulated by Addison's disease, sedation, or the natural course of cardiac or renal failure. It may be aggravated by the simultaneous loss, in mercurial diuresis, of other electrolytes, such as potassium and calcium.

The exact cause of death secondary to disturbed electrolytic homeostasis is not always a simple matter to define. In cases of salt depletion, the elevated blood urea nitrogen is contributed to by dehydration (McCance and Robinson), pre-existing renal damage in some cases, and renal impairment as a result of the mercurial diuresis (Binger and Keith). The somnolence, disorientation and stupor are cerebral symptoms and it is suggested that dehydration further compromises the impaired cerebral flow, especially in elderly patients (Jaffe et al.).

#### POSTMORTEM CHEMICAL DATA

One of the barriers to close physiologic-morphologic correlation is the frequent unavailability of data on the level of blood constituents at the time of or near the time of death. This gap may be corrected in a considerable measure by a study of the body fluids taken during the performance of a necropsy. The data so acquired, however, can not be accepted for direct interpretation at their re-

corded values because certain enzymatic and other postmortem reactions appreciably alter the antemortem values. Bacterial invasion and autolysis of tissue, abetted by high temperatures, septicemias, and the interval between the time of death and the autopsy, have an appreciable effect on the levels of these constituents and must be evaluated in individual cases.

#### Glycogen

It is estimated that 30 to 75 per cent of the glycogen disappears from tissues in the first hour after death (Yater, Osterberg and Hefke). On the other hand, glycolysis occurs in the peripheral blood because of the glycolytic action of bacteria and red blood cells so that artefactually lowered values may be expected. It is reported that increased levels of glucose have been found in the left chamber of the heart as a result of glycogenolysis of the myocardial glycogen (Naumann). It is also of interest that the postmortem level of glucose is raised in the hepatic vein and, by diffusion, in the inferior vena cava and right heart, by the process of glycogenolysis that takes place in the liver.

#### Urea, Creatinine, Uric Acid

In the case of urea, creatinine and uric acid, the postmortem values tend to be higher—at times markedly higher—than the antemortem levels. The elevation is attributed to the pre-renal azotemia resulting from terminal or agonal circulatory failure, disintegration of tissue and sepsis (Naumann, Hamilton). In one instance of a 27 year old woman with intestinal obstruction and peritonitis, the levels of non-protein nitrogen and of creatinine were 29.2 mg per cent and 1.27 mg per cent respectively one day before death, at autopsy done within 24 hours after death, the level of the blood creatinine was 7.26 mg. per cent (Hamilton).

Of the three substances, the postmortem value for creatinine most closely approximates the level before death. It is about twice the antemortem level but it represents a more reliable determination than that of urea or uric acid. The level of urea ten hours after death is about three to six times the antemortem value. The postmortem value of uric acid ten hours



FIG. A. Uremic colitis with shaggy diffluent mucosal inflammation and ulceration with blood clots.

FIG. B. Uremic ulcer (arrow) in duodenum which resulted in severe hemorrhage.

after death is also about twice its antemortem level. Cerebrospinal fluid appears somewhat more dependable than blood for these determinations, particularly for glucose (Naumann) but it is, of course, not as easily secured. The determinations of the chloride content of blood are generally agreed to be unreliable (Hamilton). Postmortem urinalysis may furnish confirmatory data.

## PATHOLOGY OF UREMIA

### *Kidneys*

As already indicated, in uremia the kidneys may show the picture of any disease which compromises a sufficient amount of parenchyma. These include the various forms of glomerulonephritis, necrotizing nephroses, acute interstitial nephritis, bilateral cortical necrosis, polycystic disease, amyloidosis, myeloma nephrosis and the different vascular diseases. Or, as in the cases of prerenal uremia, the kidneys may show no significant alterations.

### *Skin*

The skin may have a variety of lesions none of which is specific for uremia except the uremic frost. Urea crystals responsible for the "frost" are demonstrable by the xanthidol reaction. The crystals are arranged in yellowish green fine sheaves, are birefringent, and are distributed within the cutis, epidermis and appendages (plate 26). Similar crystals may be found in practically every organ from cases in which there has been a pronounced elevation of blood urea nitrogen. Other histologic reactions occasionally seen are those of pemphigus, eczema, toxic erythema and purpura.

### *Lungs*

The lungs in uremia often present a histologic picture of mild interstitial pneumonitis which is most marked at the hila. Radiologists have come to recognize that the sunburst shadows radiating from the hila of the lungs may represent the interstitial pneumonitis of uremia (plate 31 A). The differential radiologic diagnosis in these cases includes, above all, simple hilar congestion. Histologically, the picture resembles that of other varieties of interstitial pneumonitis and is characterized by mononuclear cell infiltration of the alveolar

septa, edema, histiocytes within alveolar fluid and fibrinous bands at the periphery of the alveoli (Urea crystals may be demonstrated (plate 31 B) by placing the tissue in 5 per cent solution of xanthidol in glacial acetic acid for 5 to 6 hours. The tissue is then washed in running water for 30 minutes, fixed in formalin, dehydrated thereafter in the usual manner, and cut as ordinary paraffin sections.)

### *Heart*

Sterile serofibrinous pericarditis of some degree is present in about a third of the cases of uremia (plate 27). Occasionally, the pericarditis is as striking as in a case of severe rheumatic pericarditis and is of the "bread and butter" variety. There is no relationship between the pericarditis and any underlying myocarditis. Focal nonspecific myocarditis of mild extent has been attributed to uremia. Calcification of myocardial fibers has been recorded in uremia (Scholz; Brown and Evans; Gore and Arons). The incidence of myocardial calcification in uremia is low, but when extensive, is almost always in association with uremia. Occasionally, scattered, minute foci of myocardial necrosis are found in association with hyperkalemia (plate 28 B).

### *Spleen*

For pathogenetic reasons that are not obvious, the spleen may be diffusely speckled with greyish white foci of necrosis, three to four millimeters in diameter. Such spleens are referred to as "fleckmilz" or speckled spleen or Feltis spleen. No thrombi or other organic vascular alterations account for the necrosis (plate 31 C).

### *Pancreas*

In the pancreas, dilatation of acini by inspissated secretion is seen in a mild to marked degree in about 39 to 52 per cent of cases of uremia (Baggenstoss) (plate 30 C). In only about 6 to 15 per cent of cases, however, is the lesion diffuse. This same lesion occurs in instances of severe protracted diarrhea or vomiting and is not at all specific for uremia.

### *Gastro-intestinal Tract*

Ulcers may occur anywhere along the alimentary tract from the mouth to the anus.

PLATE 30. UREMIA



FIG. A. Focal hemorrhagic lesion in uremia.

FIG. C. Uremic ulcer of colon.

FIG. B. Uremic ulcer of duodenum with underlying partially necrotic, thrombosed arteries.

FIG. D. Pancreas in uremia with dilated acini filled with inspissated secretion, a picture occurring occasionally in uremia, but also commonly with severe diarrhea, vomiting and dehydration.

The involvement may appear as discrete ulcers or as a diffuse segmental enteritis that may be grossly or histologically indistinguishable from the colitis due to bacillary dysentery, aplastic anemia or mercury colitis (plates 29, 30). Jaffé and Laing believed the ulceration to be secondary to hemorrhages into the mucosa. The ulceration may be responsible for massive fatal intestinal hemorrhages following secondary necrosis of underlying arteries. Uremia in association with hypertension may produce necrotizing arteriolitis and arteritis of bowel with subsequent ulceration and hemorrhage. The hemorrhagic diathesis of uremia may also involve the vagina with the production of hemorrhagic ulcerative colpitis.

#### Brain

Edema of the brain and meninges with focal encephalitis may occur in uremia.

#### TREATMENT OF UREMIA

Inasmuch as the precise chemical agent or agents responsible for the signs and symptoms of uremia are not known, the aim of the therapy has naturally been to restore the fluid equilibrium and the chemical composition of the blood to normal levels. This objective is accomplished by a keenly calculated addition of fluids, electrolytes, and other essential agents, abetted by vicarious excretion. Chemical imbalance is pretty much the same whatever the cause of the renal failure, so that the therapeutic objective remains essentially constant. The imbalances are the loss of water, the fall in blood calcium, the increase of phosphate and potassium, as well as of acid metabolites which lower the carbon dioxide combining power and the pH of the blood, and, of course, the azotemia. Conservative attempts should be made to correct these imbalances. Too often overcorrection, particularly of fluid and alkali restoration, is achieved with disastrous results.

The more active methods that currently have caught the fancy of workers in the field of acute renal failure are exsanguination transfusions or variants of procedures of dialysis in which an irrigating fluid of special composition is applied to peritoneal or intestinal surfaces in order to extract the retention products by the

principle of osmosis. The methods include (1) intubation and irrigation of the stomach, (2) isolation of a segment of bowel with irrigation by the dialyzing fluid, (3) peritoneal irrigation, and (4) the "artificial kidney" of Kolff which conveys the patient's arterial blood to a dialyzing apparatus and then returns the blood to the patient's vein. The composition of the dialyzing fluid is of this order:

	Gm./liter
NaCl	7.25
KCl	0.2
CaCl <sub>2</sub>	0.1
MgCl <sub>2</sub> 6H <sub>2</sub> O	0.2
NaHCO <sub>3</sub>	1.5
Glucose	10.0
Gelatin	10.0

(pH 7.4)

The great difficulty in evaluation of the therapy of acute renal failure is that a high percentage of cases recovers spontaneously, usually between the seventh to fourteenth day of uremia. Because of this fact, the nicest judgment is required for the decision as to when to replace or supplement conservative therapy with a dialyzing procedure. The skill required to carry through the dialyzing procedures without complications such as peritonitis, hemolysis, clotting, pyrogenic reactions, leaks, edema, and inadequate flow control make the decision all the more difficult. A useful and favorable survey of the subject may be found in the papers of Merrill and his associates.

Other therapeutic procedures in the treatment of acute renal failure include renal decapsulation and sympathetic block. The renal decapsulation has been performed on the assumption that the kidney in acute renal failure (e.g., mercury bichloride or hemoglobinuric nephrosis) is swollen and encased in a constricting capsule. However, the beneficial results that have been reported are more on the basis of spontaneous recovery or perhaps the resection of renal sympathetic nerves incidental to the decapsulation rather than to the relief of the effects of interstitial edema. The interference with the nerve supply has been effected with variable results by means of intravenous administration of procaine, spinal anesthesia and the block of lumbar sympathetics. Occasionally



FIG. A. *Interstitial pneumonia* of the type that may occur in uremia as well as in other conditions such as virus or rickettsial pneumonia and rheumatic fever.

FIG. B. *Xanthidrol urea crystals* (*xanthidrol reaction*) in lung of patient with uremia and "uremic pneumonitis."

FIG. C. "Flecken" or spotted spleen of Fetus with focal necrosis in uremia.

the results are striking as in the case in which the lumbar sympathetics were infiltrated with procaine with initiation of diuresis. The diuresis of 24 hours duration was followed by anuria again, so that the infiltration of procaine was repeated and diuresis promptly recurred.

The block of renal sympathetic supply is based on the theoretically sound rationale that experimental stimulation of the renal sympathetic nerves produces glomerular ischemia and resection of them results in glomerular hyperemia. The lack of adequate glomerular filtration seems by all odds the most likely immediate explanation of the oliguria or anuria in the cases of acute renal failure as opposed to the concept of complete reabsorption of adequate glomerular filtrate through necrotic tubules into the peritubular capillaries. This matter will be considered further in the discussion of the nephroses.

#### PRERENAL AZOTEMIA

Prerenal azotemia refers to the situation in which the retention products of true uremia occur for reasons not accounted for by the histologic changes in the kidneys. Nevertheless, despite the absence of significant morphologic renal alterations, there is renal insufficiency which may be of a marked degree. The conditions leading to prerenal azotemia include severe and protracted vomiting as in intestinal obstruction or eclampsia, profuse loss of intestinal contents through a fistula or by diarrhea, severe intestinal hemorrhage, some liver diseases, diabetic acidosis, various types of shock, the crises of Addison's disease, cardiac failure and dehydration.

The presence of blood in the intestinal tract, as from a bleeding peptic ulcer, often is followed by azotemia, and deserves additional comment. The increase in the level of the non-protein nitrogen after a single massive hemorrhage begins to take place in about six hours and reaches its maximum within 24 hours, but occasionally within 48 hours (Schuff and Stevens). Levels above 100 mg per cent of blood urea nitrogen have been recorded after hemorrhage into the intestinal tract (Schuff and Stevens). The elevated values for blood urea nitrogen are attributed not only to re-

sorption of the nonprotein nitrogenous products from the blood within the intestinal tract, but to the additional factors of shock, dehydration, malnutrition, and renal insufficiency which may accompany the loss of blood.

#### *Signs and Symptoms*

Notwithstanding the usual lack of conspicuous renal morphologic changes, prerenal azotemia may be accompanied by the clinical picture of uremia, such as lassitude, muscular twitching, vomiting, diarrhea, urinous breath, and coma. However, in contrast to uremia from organic renal insufficiency, pericarditis rarely accompanies prerenal azotemia.

Just as in uremia due to organic renal disease, in prerenal uremia, a rise occurs in the levels of uric acid, creatinine, and urea nitrogen, sometimes to enormous values of over 400 mg. per cent (NPN). Hypochloremia is common. Acidosis may occur in association with diabetic coma or Addison's disease, and alkalosis may result from vomiting. Oliguria and even anuria may be present although occasionally there is polyuria. The specific gravity tends to become progressively lowered. Moderate albuminuria along with some hyaline and granular casts, and a few red and white blood cells may be present in the sediment. Tests for renal function, such as urea clearance, and concentration tests, reveal abnormal function in most cases. The physiologic alterations most often responsible for the functional disturbance of the kidney in prerenal azotemia are the reduced renal blood flow, and the electrolytic imbalance of sodium and potassium particularly.

With regard to renal azotemia associated with congestive cardiac failure, it is worth noting the contributory role of the renal tubules to the aggravation of the edema due to cardiac failure. As part and parcel of the cardiac failure, there is reduced renal blood flow to about one third or one fifth of normal, while the glomerular filtration is reduced to from two thirds to one half. With the reduction of glomerular filtrate, there is not a parallel reduction in salt reabsorption, on the contrary, it is as if the tubules, receiving a diminished supply of glomerular filtrate, "pull" harder to reabsorb a disproportionate amount of salt in an at-

tempt to equal the amount of salt they reabsorb normally. The increased salt retention is a central factor leading to increased plasma volume, distention of veins and edema.

Unlike the grave prognosis of uremia caused by organic renal disease, prerenal azotemia may

be quickly resolved if the primary physiologic disturbance leading to the azotemia is cleared. This restoration is often not achieved because the basic physiologic disorder of electrolytic or fluid imbalance, or reduced renal blood flow, is recognized too late or not at all

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## 5. Malformations

The maldevelopments of the kidney, as would be expected, are concerned with (1) number, (2) size, (3) position, and (4) disorganization of architecture (plates 32, 33)

It appears generally to be true that anomalous kidneys are predisposed to inflammations of various sorts, including glomerulonephritis and pyelonephritis. It seems likely that the basis for this predisposition is the interference with urinary excretion often inherent in malplaced or rotated kidneys, especially in conjunction with anomalies elsewhere in the urinary tract.

Malformations may be classified as follows.

- Agenesis
- Hypoplasia
- Supernumerary kidney
- Ectopia
- Anomalies of fusion
- Vascular anomalies
- Anomalies of renal pelvis
- Cysts
  - Solitary
  - Polycystic

### 1. BILATERAL RENAL AGENESIA

Up to 1910, the reported cases of bilateral renal agenesis totaled 135 (Himman). Of 2100 stillbirths, agenesis occurred in 7, or 1 in 313 (Bell). Potter noted 20 cases of renal agenesis (17 in males) in 5000 autopsies on fetuses and newborn infants. Infants with this deficiency are almost always stillborn, although Rosenbaum reported the case of an infant that survived 11 days. The condition occurs predominantly in males (a ratio of about 2½ to 1) for obscure reasons, and is associated with oligohydramnios in most cases. Usually the ureters are also absent but portions of them are occasionally present. The bladder was absent in three of Bell's cases and was abnormally small in two others. All of Bell's cases were premature infants. It is worth noting that fetuses may survive to term, and even somewhat longer without any kidneys. Some other developmental anomaly, especially of the genital or-

gans, is often present. In all of Potter's cases there was hypoplasia of the lungs, and in all three females, the uterus and vagina were absent, although the fallopian tubes were present. She also observed characteristic facies in these infants with features that included (1) flattened tip of nose, (2) elongated lobes of ears, (3) receding chin, (4) prominent fold about inner canthus of the eyes, and (5) increased space between the eyes. The facies are striking, but may be observed in infants with other renal anomalies, as with polycystic kidneys (plates 32 A, 36 A). There is no relationship between the occurrence of renal agenesis and maternal age, parity, or complications of pregnancies.

### 2. UNILATERAL RENAL AGENESIA

In Bell's series of 35,329 autopsies, complete absence of one kidney occurred in 68 cases, or in 1 out of 519 cases; there was about one-half this frequency in Eisendrath's group. Single pelvic kidneys occur approximately once in 22,000 persons (Stevens). Of 2100 stillbirths, there were 16 cases of unilateral renal agenesis, or 1 in 150 (Bell). As would be expected, the greater number of cases is found among stillbirths, not because a solitary kidney is incompatible with life, but because anomalies are usually multiple, and renal agenesis is likely to be associated with other compromising anomalies. For example, of Bell's 68 cases, 16 occurred in stillbirths, 6 more were found in infants less than 1 week old. However, after this initial period was survived, the age incidence was fairly evenly distributed through all decades.

Unlike the sex incidence of bilateral renal agenesis, there is no significant difference in the frequency of solitary kidney in males and females below one year of age, although the predominant incidence in males (about 2 to 1) is manifest after that period (Bell). Agenesis, again for reasons unexplained, is somewhat more likely to occur on the left side than on the right, for example, in Collin's large series, the left kidney was absent in 51.7 per cent and the right in 40.9 per cent. (14 per cent not stated).

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  - Polycystic

### 1. BILATERAL RENAL AGENESIA

Up to 1940, the reported cases of bilateral renal agenesis totaled 135 (Hinman). Of 2400 stillbirths, agenesis occurred in 7, or 1 in 343 (Bell). Potter noted 20 cases of renal agenesis (17 in males) in 5000 autopsies on fetuses and newborn infants. Infants with this deficiency are almost always stillborn, although Rosenbaum reported the case of an infant that survived 11 days. The condition occurs predominantly in males (a ratio of about 2½ to 1) for obscure reasons, and is associated with oligohydramnios in most cases. Usually the ureters are also absent but portions of them are occasionally present. The bladder was absent in three of Bell's cases and was abnormally small in two others. All of Bell's cases were premature infants. It is worth noting that fetuses may survive to term, and even somewhat longer without any kidneys. Some other developmental anomaly, especially of the genital or-

gans, is often present. In all of Potter's cases there was hypoplasia of the lungs, and in all three females, the uterus and vagina were absent, although the fallopian tubes were present. She also observed characteristic facies in these infants with features that included (1) flattened tip of nose, (2) elongated lobes of ears, (3) receding chin, (4) prominent fold about inner canthus of the eyes, and (5) increased space between the eyes. The facies are striking, but may be observed in infants with other renal anomalies, as with polycystic kidneys (plates 32 A, 36 A). There is no relationship between the occurrence of renal agenesis and maternal age, parity, or complications of pregnancies.

### 2. UNILATERAL RENAL AGENESIA

In Bell's series of 35,329 autopsies, complete absence of one kidney occurred in 68 cases, or in 1 out of 519 cases, there was about one-half this frequency in Eisendrath's group. Single pelvic kidneys occur approximately once in 22,000 persons (Stevens). Of 2400 stillbirths, there were 16 cases of unilateral renal agenesis, or 1 in 150 (Bell). As would be expected, the greater number of cases is found among stillbirths, not because a solitary kidney is incompatible with life, but because anomalies are usually multiple, and renal agenesis is likely to be associated with other compromising anomalies. For example, of Bell's 68 cases, 16 occurred in stillbirths, 11 more were found in infants less than 1 week old. However, after this initial period was survived, the age incidence was fairly evenly distributed through all decades.

Unlike the sex incidence of bilateral renal agenesis, there is no significant difference in the frequency of solitary kidney in males and females below one year of age, although the predominant incidence in males (about 2 to 1) is manifest after that period (Bell). Agenesis, again for reasons unexplained, is somewhat more likely to occur on the left side than on the right, for example, in Collin's large series, the left kidney was absent in 54.7 per cent and the right in 40.9 per cent. (4.4 per cent not stated).

The absence of the kidney may be associated with various conditions of the corresponding ureter, and ureteral orifices. The ureter is completely absent in most cases. In some, there is evidence of a vestigial ureteral structure, varying from a dimple in the bladder to a structure extending for a length of several centimeters, and rarely for the entire distance of a normal ureter. In most cases, the ureter is reduced to a fibrous cord. Occasionally it ends ectopically in the seminal vesicle. The renal artery and vein do not develop. The ipsilateral adrenal gland is stated to be present in 75 per cent of cases (Eisendrath), in many instances there is no mention of the adrenal gland in the autopsy protocol.

Associated anomalies of other organs are present in the majority of cases. In adults, according to Fortune, about two thirds of the females had malformations of the genital tract, such as bicornuate uterus or atretic vagina. In the male there is often absence or anomalies of the epididymis, ductus deferens, seminal vesicles and ejaculatory duct on the side of agenesis of the kidney. Bell found very few anomalies associated with solitary kidney in adults; the infants were most affected and exhibited spina bifida, meningocele, imperforate anus and other maldevelopments.

#### MORPHOGENESIS OF RENAL AGENESIA

The morphologic basis of renal agenesis would seem theoretically to result either from a lack of metanephrogenic primordium from the nephrogenic cord, a failure of the ureteral bud to develop from the wolffian duct, or a lack of proper contact ("organizer" influence) between the ureteral bud and the nephrogenic cord. Presumptive clues derived from associated anomalies, such as frequent absence of ureter and ductus deferens point to the wolffian duct

as the source of the dysembryogenesis. As Boyden indicates, there is likelihood that the wolffian duct does not reach the cloaca and, to be sure, renal agenesis may be produced experimentally in embryos by interrupting the wolffian duct. This same mechanism may account for unilateral as well as bilateral renal agenesis. Often, renal hypoplasia is mistaken for agenesis, an error that may be avoided by sectioning the remnants of tissue in the renal fossae, and discovering vestiges of atrophic or poorly developed nephrons.

#### STATUS OF THE SOLITARY KIDNEY

The solitary kidney is usually considerably larger, and often twice the weight of a normal kidney. The enlargement is teleologically attributed to a compensatory hypertrophy and is so frequent in solitary kidneys that encountering a large otherwise normal appearing kidney should recall the possibility of the absence or hypoplasia of the opposite organ. The solitary kidney is usually in the normal position, but is occasionally found in the iliac fossa and the true pelvis, and in some instances is abnormally rotated.

The general tendency of the predisposition to inflammation of anomalous kidneys applies to the solitary kidney too. In this case, the predisposition may be enhanced by associated anomalies of renal vessels or of the ureter, leading to interference with drainage of urine. Of Bell's 68 cases of congenital solitary kidney, there were four with hydronephrosis, and four with duplication of the ureter. In the absence of any untoward inflammation, the solitary kidney is able to maintain renal sufficiency inasmuch as the "factor of functional safety" of the kidneys is about 5 to 1. However, Nation found that in 6 out of 27 cases of unilateral renal agenesis,

FIG. A. *Facies characteristic of infants with renal agenesis including prominent caudal fold, large low set ears, receding chin and flattened nose*

FIG. B. *Bilateral renal agenesis. Black dots beneath adrenals indicate vestigial kidneys.*

FIG. C. *Unilateral renal agenesis, occasionally associated with one or two rudimentary ureters*

FIG. D. *Unilateral renal hypoplasia*

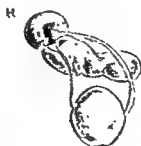
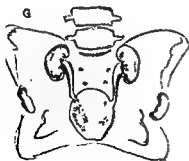
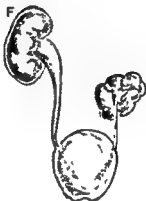
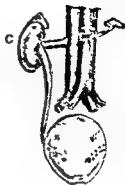
FIG. E. *Ectopic kidney over aorta. Ureter in midline*

FIG. F. *Unilateral renal pelvis ectopia*

FIG. G. *Bilateral renal pelvic ectopia*

FIG. H. *L-shaped kidney (fused)*

FIG. I. *Sigma shaped kidney (fused).*



(Legends on facing page)

death was caused by renal insufficiency, produced in 3 of these by "congenital inadequacy."

### UNILATERAL RENAL HYPOPLASIA

Unilateral renal hypoplasia occurred 77 times in 63,076 autopsies, or 1 in 816 (Eisendrath). The unequivocal determination of the pathogenesis of a single dwarfed kidney is often impossible to achieve. The reason for this difficulty is that the end stages of renal inflammation occurring early in life may be indistinguishable from congenitally hypoplastic kidneys. The decision as to what the upper weight limit of a hypoplastic kidney should be is an arbitrary one and has been set at 60 grams by Bell. Within this weight limit will be included not only congenitally hypoplastic kidneys but also instances of unilateral chronic pyelonephritis and kidneys whose blood supply has been compromised by trauma or disease. In addition, of course, some kidneys with chronic pyelonephritis, chronic glomerulonephritis, and benign nephrosclerosis may undergo so marked a degree of bilateral contraction that they fall within the weight range of hypoplasia. The gross and histologic criteria for the diagnosis of glomerulonephritis, pyelonephritis and nephrosclerosis are described elsewhere. However, it is apparent that these three conditions, particularly the first two, may be superimposed on a congenitally hypoplastic kidney and so obscure the diagnosis.

True congenital hypoplasia of the kidney may take one of the following forms:

1. Miniature replicas of adult kidneys, with, however, fewer reniculi or lobes, for example, 3 to 5 rather than a normal number of about 12 to 18 (plate 72A). The number of calyces is correspondingly reduced. The glomeruli tend to be large and the tubules dilated. Correspondingly, urography would reveal a triangular or ampullary pelvis leading into minor calyces without

intermediate major calyces, or the pelvis would be small and show only one or two calyces. It has been suggested that if the pelvis is small and shows only one or two calyces, it is a miniature replica of the adult kidney.

nephrogenic mass is another possibility.

2. Single or multiple cysts, dilated tubules and more or less intervening fatty, fibrous or calcified interstitium often with sclerotic arteries (plates 40, 41).

Additional features to consider are the size of the renal pelvis and the renal arteries. If the renal pelvis is disproportionately large in comparison with the parenchyma, atrophy due to hydronephrosis obviously must be suspected. Similarly, if the appertaining renal artery was originally (prior to endarteritis of disuse) of a caliber larger than that anticipated for the size of the organ supplied, the presumption is that the kidney became atrophic for reasons other than dysembryogenesis.

The functional capacity of the congenitally hypoplastic kidney naturally varies with the amount of residual parenchyma, but, at best, the small organ, by itself, may be assumed to be incapable of sustaining life. In some instances, the unilateral hypoplastic kidney with a normal opposite kidney has been associated with and perhaps responsible for hypertension (Higbee). Nation differentiates the hypoplastic from the aplastic kidney on the basis of evidence of the total lack of function of the latter from its beginning.

### BILATERAL RENAL HYPOPLASIA

There are numerous reports of marked hypoplasia of both kidneys, which, as in bilateral agenesis, is associated, as a rule, with stillbirth. Cases of lesser severity survive several months or a few years until death occurs in uremia, often accompanied by rickets and by poor or dwarfed development of the child. As indicated,

FIG. A Horseshoe kidney (fused)

FIG. D. Crossed ectopia with out fusion.

FIG. G. Anomalous renal vessels with constriction and hydronephrosis

FIG. B. Caudal kidney (fused)

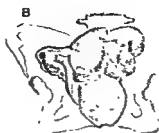
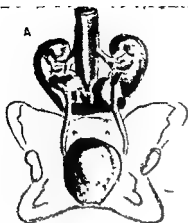
FIG. E. Ectopia of hypoplastic kidney in bladder wall with contralateral hydronephrosis

FIG. H. Extra-renal pelvis.

FIG. C. Crossed ectopia with fusion.

FIG. F. Faulty rotation of right kidney.

FIG. I. Polycystic kidney



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A

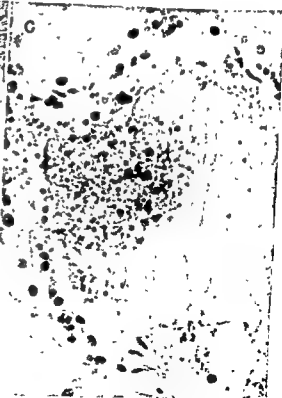


FIG. A Solitary cyst of kidney. The evidence suggests that these are acquired rather than congenital.

FIG. B Partially calcified wall of large cyst of kidney which could be visualized radiographically.

FIG. C. Small solitary intraparenchymal cyst with partially calcified contents.

A



B



FIG. A. Solitary cyst of kidney

FIG. B. Solitary cyst showing epithelial lining resembling that of a distal convoluted tubule

when the so-called congenital bilateral hypoplasia of kidneys of adults are carefully screened, it is found that very few are left after the small contracted kidneys of chronic glomerulonephritis, chronic pyelonephritis and benign nephrosclerosis are removed

### SUPERNUMERARY KIDNEY

One of the rarest of renal anomalies is the supernumerary kidney. Until 1944, 46 such instances had been reported (Exley and Hotchkiss). The term "supernumerary kidney" should be reserved for a third kidney which is entirely free from its adjacent kidney or only loosely attached. It may lie above the normal kidney, but usually lies inferiorly and occasionally in the pelvis. This definition distinguishes the supernumerary kidney from the fused kidney or double kidney. The blood supply is variable and tends to be derived from the closest arterial source, such as the aorta, or normal renal artery. In the majority of cases, the ureters of the supernumerary and ipsilateral kidney fuse somewhere along their course, commonly just proximal to their entrance into the bladder. However, the ureters may be reduplicated so that three ureteral orifices may be present. Occasionally the third ureter ends in the vulva, vagina, or prostatic urethra.

The supernumerary kidney is smaller than normal unless enlarged by hydronephrosis, cyst or neoplasm. The first authentic case of adenocarcinoma in such a kidney is stated to be that of Exley and Hotchkiss.

#### *Embryogenesis of Supernumerary Kidney*

The supernumerary kidney arises presumably because of the development of a second ureteral bud from the mesonephric duct, which then is able to make contact with a portion of the primordial nephrogenic mesenchymal tissue. If the two ureteral buds arise in close enough proximity to each other, they may then invade their single overlying metanephrogenic cap to form fused or double kidneys.

### ECTOPIA OF KIDNEYS

Congenitally displaced kidneys in most instances lie in the iliac fossa, on the brim of the pelvis, or in the pelvic cavity, a few are dis-

placed to the midline or to the opposite. Renal ectopia occurs in a ratio of approximately 1 to 750 autopsies without selective evidence. There is a greater incidence of distortions of size and shape in those ectopic kidneys that are in the pelvic cavity than in those located more superiorly in the iliac fossa. Possibly the pressure of adjacent organs on displaced kidneys lacking the normal fatty cushion is a factor in their altered shape. The renal pelvis is usually directed ventrally although some are dorsally. Often the ectopic kidney is congenitally hypoplastic; occasionally both kidneys are displaced and fused. A congenitally solid kidney may also be displaced in the pelvis. The ureter tends to be short and because of its position, vulnerable to obstruction. The arteries of the ectopic kidney in most instances arise from the adjacent portion of the aorta or iliac arteries and rarely from the normal level in the aorta. The veins drain into nearby veins (Harris).

The ectopic kidney is subject to the same ordinary complications of the normal kidney. However, by virtue of its disadvantageous position, from the point of view of pressure by adjacent organs on the ureter, hydronephrosis, pyelonephrosis, pyelonephritis and nephrolithiasis are particular hazards. In the presence of any of these complications, it is obvious that the clinical picture may simulate gynecologic disorders, or bowel involvement, such as appendicitis. In some instances, a pelvic kidney has been responsible for serious dystocia. The diagnosis of ectopic kidney has been made by the observation of abnormally located shadows of calcium in the flat-plate, with urography, and by palpation of a mass behind the uterus (Coppridge).

### CROSSED ECTOPIC KIDNEY

The crossed ectopic kidney is distinguished from the double kidney and the fused horseshoe kidney (i.e., the kidney of median fusion). In the case of crossed ectopia, the renal bladder becomes deviated to the opposite side where it usually lies caudal to the normal or "fixed" kidney. The ectopic kidney may develop separately or may become completely fused with obliteration of the lines of demarcation. T

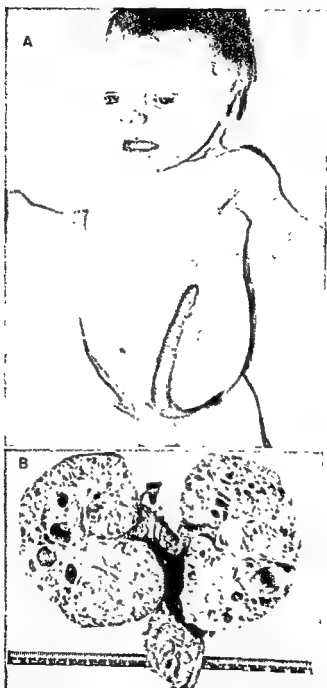
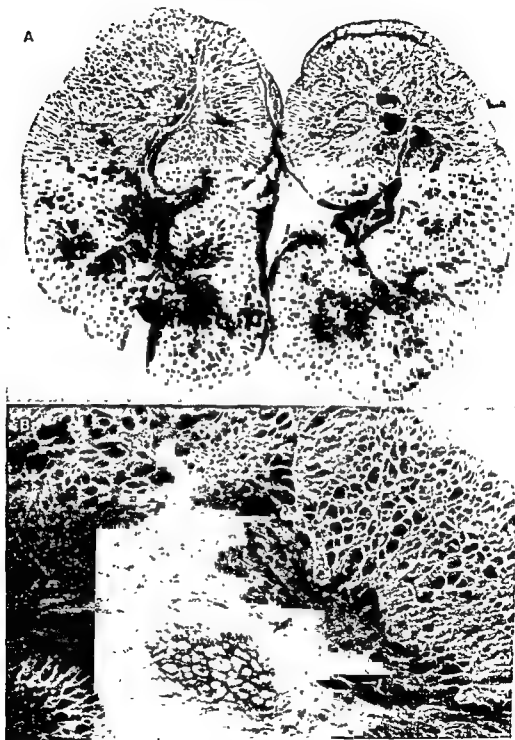


FIG. A Two week old infant with bilateral polycystic kidneys indicated by abdominal markings and illustrated in figure B. This infant has the facies described in cases of renal agenesis: the prominent fold about the inner canthus, the receding chin, the flattened tip of the nose, and the enlarged ears.

FIG. B Polycystic kidneys from infant in figure A.

PLATE 37. CONGENITALLY POLYCYSTIC KIDNEY



FIGS A AND B *Infantile polycystic kidney* in two magnifications showing the diffusely and regularly honeycombed appearance which is the usual appearance of the polycystic kidney of infants, as opposed to adults. Too much parenchyma is destroyed to permit survival to adult life. (Courtesy of W. A. D. Anderson. From *Pathology*, St. Louis, C. V. Mosby, 1948.)



FIG. A *Honeycombing of infantile congenitally polycystic kidney from type illustrated in figures A and B, plate 37*

FIG. B *Higher magnification of polycystic kidney illustrated in figure A.*

FIG. C. *Congenitally polycystic liver associated with polycystic kidney of figure B. Cysts appear to arise from bile ducts*

hilum may face in any of a variety of directions depending on the degree of rotation of the kidneys. The so-called "fixed" kidney may also show an abnormal position of its hilum. The ureters do not unite but terminate in separate ostia, generally in the normal position in the bladder. Inasmuch as it is the caudal kidney that is usually the ectopic one, its ureter crosses the midline to end in the ureteral orifice of the opposite side. In its passage to the bladder, the ureter may take an abnormal route, sometimes coursing behind the rectum.

As with many other anomalies of the kidneys, there is no diagnostic symptomatology associated with crossed ectopia. However, the importance of ascertaining the existence of a fused ectopic kidney when nephrectomy is under consideration is obvious. In the great majority of instances, the length of the fused ectopic kidney, which is greater than normal, offers by itself some clue as to diagnosis. The presence of a line of demarcation between the two fused kidneys is additional presumptive evidence, but considered alone this does not differentiate crossed ectopia from fused double kidney. In the instance of fused double kidney not only are the pelves reduplicated, but the ureters of each kidney may have separate ureteral orifices. If the reduplication is incomplete, however, only a single orifice may be present. Occasionally, the ureteral opening of one of the ureters may be extravascular, rarely, there may be three ureteral orifices on one side of the bladder. The fused double kidney appears to be predisposed to hydronephrosis which may be sharply limited to one half of the organ.

#### HORSESHOE KIDNEY

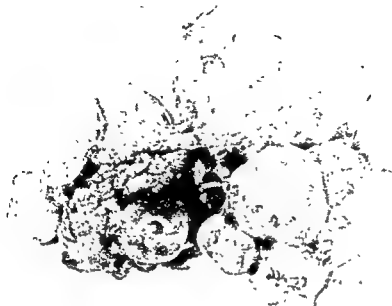
The horseshoe kidney, the "cake" kidney and the L-shaped, or sigmoid kidney all represent essentially variants of the anomaly of median fusion. The incidence of horseshoe kidney is variously reported as occurring in from 1 in 715 autopsies to 1 in 376 (Bell). As in other instances, the overall incidence of anomalies varies with the proportion of infants in the autopsy sample inasmuch as the frequency of anomalies is considerably greater among stillbirths and the early age groups than in older series (e.g. horseshoe kidney, 1 in 216 in infants below one year of age) (Bell).

The horseshoe kidneys are believed to result from fusion of the renal blastemas at about the eighth to tenth fetal week, at which time the lower poles of the kidneys are in close proximity. Actually, approximately 10 per cent of horseshoe kidneys are fused at their upper poles, the remainder being joined at the inferior poles. The most common level at which horseshoe kidneys are located is close to the region of the bifurcation of the aorta, between the 3d and 5th lumbar vertebrae; occasionally, they are found at the normal level of the kidney, at the promontory of the sacrum or even in the true pelvis.

The long axes of normal kidneys are directed obliquely downward and outward whereas in the horseshoe kidney the axes are directed obliquely inward. As a result, the shadows of calculi in the anomalous kidney are correspondingly situated. The pelves are generally on the anterior aspect of the kidney although often there is no pelvis proper but rather extrarenal calyces which join to form the ureter. The isthmus or site of fusion of the two kidneys may have its own calyx or calyces. Reduplication of pelves is not rare. The pyramids are arranged in a frontal rather than sagittal plane, so that some of the calyces are directed mesially. In about one third of the cases, there is one artery for each half of the anomalous kidney, in the remainder there are multiple arteries. The ureters which usually pass in front of the isthmus, diverge from the midline for a greater distance than normal. This feature may be of diagnostic importance. In some instances, ureters arise from the isthmus. The course of the ureter in front of the isthmus, its occasional fixation to that structure, and the frequent presence of accessory vessels are factors predisposing toward obstruction of urinary outflow, and pelvic infection.

Renal calculi are more common in the horseshoe kidney than in the normal kidney. They were found in 29.5 per cent of 108 cases (Rathburn); both pelves were involved in about 3 per cent of cases. There is no specific symptomatology of the horseshoe kidney but the position of this organ tends to produce a clinical entity known as the *Rovsing syndrome*. The syndrome is attributed to pressure of the isthmus on underlying abdominal nerves and ves-

A



B



FIGS. A AND B. *Irregular variants of congenitally polycystic kidney from infants aged six months (figure A) and two weeks (figure B). Both of these cases showed unilateral involvement. The term "multicystic" is often used instead of "polycystic," without special etymologic justification to refer to these irregularly lobulated, misshapen, congenitally cystic kidneys. The photomicrographs of figures A and B are shown in plate 40, and are to be contrasted with those of the usual honey-combed variety of plates 37 and 38.*



sels resulting in upper abdominal pain when standing or sitting, particularly after changing from a supine position. Such patients may learn to lean forward when walking, a position that effects some relief of pressure from the isthmus. Hyperextension of the back, eating heavily, or lifting may produce exacerbation of the pain, which, in a few cases, simulates a tabetic crisis. Symphysiotomy or division of the isthmus has given relief in some cases.

#### ANOMALIES OF RENAL PELVIS

The renal pelvis participates, of course, in the faulty rotation of the kidney and may lie in any plane from a ventral to a dorsal position. As indicated, abnormal rotation occurs in variants of the horseshoe kidney, in double kidneys and in ectopic kidneys. The clinical recognition of abnormal rotation is of importance in operations where orientation particularly with regard to anomalous blood vessels is helpful.

##### *Double pelvis*

Double pelvis occurs with a frequency of approximately 1 in 150 autopsies. Some authors consider a double pelvis indicative of a double fused kidney in which the isthmus may or may not be evident. The double pelvis may be associated with complete or incomplete duplication of ureters.

##### *Extrarenal pelvis*

These may occur in association with normal kidneys, as well as with horseshoe kidneys, ectopic, hypoplastic and double kidneys. The pelvis and calyces are quite clear of the renal parenchyma. In some instances, the ureter is formed directly by the union of calyces with the intermediary pelvis. The evidence that extrarenal pelvis may lead to hypertension is not at all satisfactory.

#### ANOMALOUS RENAL VESSELS

Anomalous renal vessels are of importance because of the difficulty they may cause

through hemorrhage and infarction by inadvertent tearing or ligation during operations, and because of the ureteral obstruction and hydronephrosis they may produce. The anomalies take the form of upper or lower polar arteries from the aorta or the main renal artery, as well as multiple (2, 3 or 4) main renal arteries. There is some difference of opinion as to whether or not ligation of a polar artery may be done without hazard. It is a fact that ligation of some polar arteries does produce anemic infarcts, so that the size of the vessel and available collateral circulation must be the determining factors. Upper polar arteries are found in about one of seven kidneys and lower polar arteries about half as frequently. The lesser incidence of lower polar arteries is fortunate because they, rather than the upper ones, may obstruct the ureters. The anomalous vessels are usually accompanied by veins. Rarely are the veins present alone, and rarely is a vein responsible for ureteral obstruction. The ureter may be obstructed by anomalous vessels at the pelvis proper, at the ureteropelvic junction, and in the lumbar and pelvic portions. Nephroptosis is occasionally a contributory factor in the mechanics of ureteral obstruction. The symptoms and hydronephrotic effects of arterial compression of a ureter will of course depend on the degree and persistence of occlusion, and the supervision of infection.

#### CLASSIFICATION OF CYSTS

##### *Solitary cysts*

- Serous cysts
- Dermoid cysts
- Endometrial cysts
- Parapelvic lymphatic cysts
- Echinococcus cysts

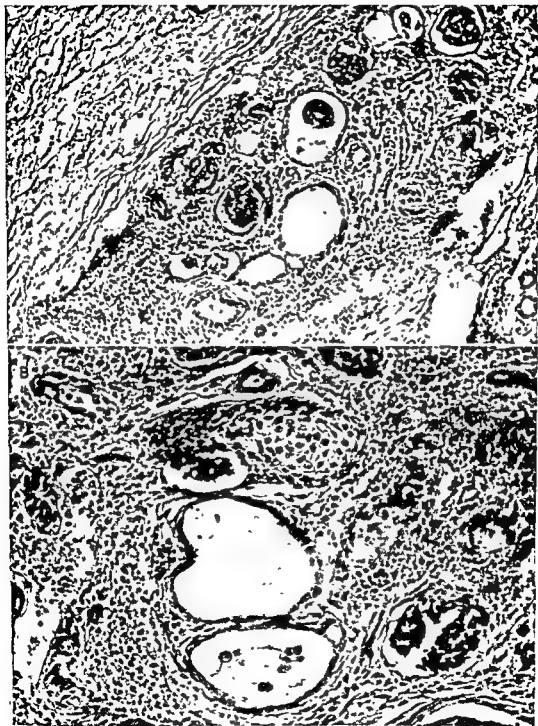
##### *Polycystic*

- Congenital
  - Infantile type
  - Adult type
- Acquired (retention cysts of contracted kidney)

FIG. A. Congenitally polycystic kidney illustrated in figure A, plate 39. Much fibrosis is present about more or less complete nephrons in some of which there is the suggestion of partial obstruction.

FIG. B. Plate 39 A

of cartilage (resembling squamous figures A and B seems fundamental in plate 33



(Legends on facing page)

### SOLITARY (SIMPLE) CYSTS

*Solitary* (simple) cysts of the kidney generally refer to single thin walled, fairly large cysts, averaging 5 to 10 cm in diameter, filled with clear, serous, colorless or light amber fluid and located usually unilaterally at the upper pole in about 23 per cent of the cases, the lower pole in 68 per cent and occasionally in the central portion (8 per cent) (Braasch and Hendrick) (plate 34). Some of the cysts are multiloculated, but the difference is not basic. Solitary cysts are found in about 3 to 5 per cent of autopsies, they occur equally between both sexes and are commonest in the group between 35 and 50 years of age. Solitary cysts are rare in infants and children, a fact that suggests the cysts represent an acquired rather than a congenital lesion. Solitary cysts may occasionally occur from infarction or traumatic atrophy, and from echinococcus infection.

These cysts are lined by single layered, flat or cuboidal epithelium resembling tubular epithelium. The fluid of the serous cyst may contain albumin, leucine, cholesterol from old blood, salts, calcium and traces of urea (plates 34, 316 B). The adjacent parenchyma is compressed and transformed into a fibrous capsule (plates 34, 35).

The cysts are most often clinically dormant although symptoms may arise from pressure, rupture, hemorrhage or infection. Hematuria is present in less than 10 per cent of cases (Hirshman). Occasionally, the wall of the cyst may become calcified (plate 34 B) and on that account may be visible in a roentgenogram. The main differential problem is the distinction of the cysts from neoplasms and hydronephrosis. Occasionally, a papillary adenoma arises in a solitary cyst (plate 273).

Multiple small, thin walled serous cysts, averaging 2 to 10 mm are frequently found in gout and in other nephrosclerotic kidneys secondary to arterial and arteriolar sclerosis. These are regarded as *retention cysts* with somewhat more conviction than are the large solitary cysts.

*Dermoid cysts* of the kidney occur rarely. (Valentine, 1929, collected eight from the literature and added one of his own.) The n-  
tain hair, keratin and sebaceous

together they resemble the dermoids that arise in other locations, for example, the ovaries. They are benign. The dermoid cyst may be grossly simulated by old hemorrhage into a solitary cyst, or by cystic degeneration of an intrarenal encapsulated hematoma in which the old blood has become a grumous mass of cholesterol and hemosiderin (plates 281, 315B).

Only one case of cystic *endometrial tumor* within the kidney has been recorded (Marshall plate 281).<sup>\*</sup> Echinococcus cysts occur rarely in this country but are not uncommon in Australia. *Paraneuric cysts* are usually considered to be lymphogenous, some undoubtedly are tubular or pyogenic. They may be simple or multiple (plate 316 A). Further description of the latter three types of cysts is in chapter 14.

### POLYCYSTIC KIDNEYS

As with other anomalies the incidence of polycystic kidneys is dependent on the age distribution of the patients autopsied. Combined statistics collected from the literature show an overall incidence of approximately 1 in 350. In 240 stillbirths, the incidence was increased to 1 in 200 (Bell). There is no difference in sex incidence unlike the situation found in bilateral renal agenesis. There is a distinct heredito-familial predisposition.

Not all cases of congenital polycystic kidney are bilateral. Contrary to the general impression of its infrequency, unilateral polycystic kidneys have been variously reported as occurring in 4 to 13 per cent of cases (Rall and Odel).

The bilaterally involved polycystic kidneys are likely to be of approximately the same size, although occasionally there is considerable difference in their size and weight. As a matter of fact, several examples are revealed in which a large polycystic kidney was removed on the assumption that the opposite kidney was uninvolved because of its normal size; this presumption was proved to be in error when cysts of the remaining kidney enlarged or its polycystic nature was discovered years later. On this account clinical data on the incidence

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eported (Maslow, L. A., and  
osm of the Kidney J. Urol.



FIG. A. Hypoplastic kidney with multiple cysts, some filled with calcified material

FIG. B. Hypoplastic kidney with multiple cysts of the variety illustrated in plate 39 (A.F.I.P. Acc. 416376)

Less marked degrees of atrophy of the parenchyma and formation of cysts occur than those indicated above, leaving sufficient parenchyma to carry on normal function. The latter cysts form the subclinical group which survive and which may remain undiagnosed until necropsy (plate 43 B, C). Most of the cysts are filled with thin watery fluid which may be colorless or light yellow, or different shades of brown from old hemorrhage, some contain frank blood or exudate (plate 316B). The lining of the cysts is smooth, except for occasional papillary projections and trabeculations (plate 273), the walls are usually thin, but vary somewhat in thickness, depending on the amount of fibrotic atrophy of the parenchyma about them. At the surface, the walls of the cysts are thin enough to be translucent and are easily broken. The fluid of the serous cysts contains a high content of urea, uric acid and creatinine, as well as some globulin. The correlation with the levels of these substances in the blood requires further documentation. The calyces are rather characteristically deformed and elongated. This deformity is best observed in molds or in urographic films. In advanced cases, the pelvic pattern is bizarre due to the lengthening and compression of the major and minor calyces, so that the term "dragon deformity" is applied to the radiographic picture. The normal cupping at the end of the minor calyces may be flattened or expanded. The cysts may communicate with the calyces although most do not. The polycystic kidney may be associated with other renal anomalies such as double pelvis, double ureters, ectopia, and hamartomas of other organs such as the brain, cord, meninges, skull, vertebral column, liver and pancreas.

There appears to be a significant association of polycystic kidneys with polycystic livers (33 per cent) (plate 42), and occasionally with polycystic pancreases (9 per cent) (Rall and Odel).

### *Histologic appearance*

The cysts are almost constantly distributed from cortex to medulla, and show no predilection for one part of the kidney except in rare in-

stances as mentioned. The smallest of the cysts are about the diameter of convoluted tubules. They are lined by cuboidal epithelium which is often flattened, so as to resemble endothelium. The contents, as a rule, comprise delicate strands and granules of protein precipitate, some of the cysts have dense clumps of acidophilic precipitate, blood, hemosiderin macrophages, calcium deposits and purulent exudate. In a few cysts there are papillary, epithelial covered, fibrous invaginations of the wall. The latter is occasionally thickened by a fibrous rim, apparently the result of parenchymatous atrophy due to expansion of the cysts. The intervening parenchyma varies in amount from case to case and from field to field in the same slide. There is nothing characteristic about this parenchyma, and in the regularly polycystic kidney if the parenchyma were viewed apart from the cysts it would be impossible to determine the nature of the basic lesion (plate 43A). This intervening parenchyma is frequently modified by arteriosclerosis and especially arteriolosclerosis in the adult. Glomerulonephritis, pyelonephritis and occasionally even neoplasm may occur just as they may in any other kidney.

As mentioned, one form of the infantile polycystic kidney, sometimes referred to as "multicystic" kidney, is composed of markedly irregular cysts and is unilateral. This type shows a histologic picture essentially different from that just described. The gross and histologic features are illustrated in plates 39 and 40. In addition to cysts which may vary markedly in size, there are isolated little islands of nephrons in different stages of atrophy, separated by stroma far more abundant than the more usual infantile or adult forms of congenital polycystic kidney. Small bland foci of hyaline cartilage may be seen in relation to these units (plate 40 B). As stated, these unilateral irregularly polycystic kidneys may be markedly diminished in size (plate 41) with much fibrosis, calcification and even ossification and often with rudimentary collecting tubules lined characteristically with tall epithelium (plate 41 B). The ureter of this form of polycystic kidney may be absent or atretic (Goodyear and Beard).



FIG. A Histologic section of congenitally polycystic kidney of adult demonstrating a moderate amount of parenchyma between the cysts. The intervening parenchyma is essentially normal appearing in contrast to that of the infantile "multicystic" kidneys (plates 39-40).

FIG. B Congenitally polycystic kidney of an adult with abundant parenchyma between cysts. Histologic picture in figure C.

FIG. C Section of kidney illustrated in figure B, showing considerable residual parenchyma so that renal insufficiency was averted.

### Treatment

The complications of cystic rupture with perinephritis, the occurrence of hemorrhage or of suppuration in cysts, or the presence of calculi may require major surgery. However, the uncomplicated polycystic kidney has been treated by puncturing the cysts with or without marsupialization, injections of sclerosing agents into the cysts, or splitting the kidney down to the calyces. The benefits of these forms of therapy are debatable and many prominent urologists are opposed to the use of sclerosing solutions for the cysts. In some instances, the function of one of two involved kidneys is poor while the other is adequate. In such a situation, nephrectomy of the worse kidney has appeared beneficial, although many urologists oppose this procedure too.

### Embryogenesis

Two principal competitive theories have been proposed to account for the formation of the cysts. According to the theory of Rubbert, the primordium of the secretory or cortical portion of the nephron, after it becomes canalized, fails to join the lumen of the collecting portion which arises separately from ramifications of the ureteral bud. It is assumed that the "blind secretory" part of the proximal nephron secretes fluid which is dammed up and results in cystic dilatations.

The second theory (McKenna and Kampmeier) postulates that the early generations of secretory tubules, which normally become cystic and disappear, persist, for some reason, to become progressively enlarging cysts. The objection to this theory is that these early generations of cysts occur in the zone nearest the medulla and farthest from the ultimate cortical capsule. It would therefore be expected that such cysts, if they persisted, would show some corresponding semblance of zonal distribution. Actually with few exceptions, the cysts of the polycystic kidneys are equally distributed throughout the kidney.

Both of these theories, different as they are, might perhaps be embellished with the additional consideration of the pathogenetic role of defective integration of the inductive influence of Spemann's "organizers" or specialized

sentinel cells. And yet, the issue that remains still concerns the histogenesis of the defect and neither of these ingenious but opposing theories quite answers the assignment. For this reason, both enjoy fairly equal popularity despite their disparity.

No constructive suggestion is here offered except possibly one based on our somewhat different concept of the embryology of the nephron as outlined in chapter 1. From a study of serial sections of the kidneys of human fetuses from 9 mm. in length to full term size (plates 1-6), the impression is gained that the proximal and collecting portions of the nephron do not develop *pari passu* as two separate tubules with subsequent junction of their lumens into a single tubule, as a pedicle flap might be joined into a receptor site. Rather it is our impression that the tubule from the original ureteral bud elongates, branches and extends into the active multipotent primordial cells of the subcapsular blastema and progressively forms the proximal portion of the nephron from these cells (plate 6). In other words, the glomerulus and proximal tubules are the youngest portion of the nephron not merely because these structures require the stimulus from the collecting tubules to be molded and shortly to be welded to them. They are the youngest because, cell by cell, they are built onto the buds of the more distal portions of the nephron advancing into the subcapsular metanephric mass. On this account, we believe that the cysts of the polycystic kidney develop not from a failure of the two segments to meet and form a common lumen, but from an atresia or failure of canalization at different levels along the nephron. As a result, cysts occur at various levels of the same and different nephrons. Congenital atresia is a relatively common phenomenon and probably also occurs in the intrahepatic biliary ducts to cause cysts there, and in the pancreas to produce cysts in that organ. The distorted influence of organizers is surely conceded to be the basic fault in the causation of the atresia as it is in other histogenetically unrelated anomalies such as spina bifida, meningocele, anencephaly and others. It is the explanation or structural translation of this influence that is under dispute, as just indicated.

PLATE 44. CONGENITALLY POLYCYSTIC KIDNEY, ADULT TYPE



FIG. A Congenitally polycystic kidney of an adult with suppuration in the cysts. Histologic sections in figures C and D.

FIG. B Congenitally polycystic kidneys of an adult demonstrated by retrograde pyelography.

FIGS. C AND D. Purulent exudate in cysts of kidney illustrated in figure A.



PLATE 45 HYDRONEPHROSIS, CONGENITAL

A



B



C



D



FIG A Congenital hydronephrosis and hydroureter due to urethral obstruction

FIG B Congenital hydronephrosis

FIG C Congenital hydronephrosis, hydroureter, double ureter and fused kidneys

FIG D Congenital hydronephrotic atrophy with hydroureter

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## 6. Diseases of the Glomeruli

### INTRODUCTION

APART from matters of prevention and therapy, the problems in glomerulonephritis are concerned not so much with its diagnosis as with the understanding of its natural evolution in terms of physiologic pathology. After all, the diagnosis of glomerulonephritis is generally established with relative ease on the basis of hematuria, albuminuria, edema and other adjuvant signs and symptoms. But certain key phenomena are unexplained. For example, why does blood escape into the urine in abundance in some cases and not at all in others in which glomeruli seem equally or more damaged? Similarly, what is there about the glomerulitis that causes the urine in some instances of glomerulonephritis to boil solid with albumin while only slight loss of albumin occurs in others? Why is there tubular dysfunction in only a portion of the cases of glomerulonephritis without apparent relationship to the glomerular changes? What mechanisms cause certain kinds of glomerulonephritis to become relentlessly progressive while others are completely resolved? How equivocal is the evidence that "lipoid nephrosis" is really a form of diffuse glomerulonephritis, and is it possible to know merely from histologic examination that the patient's illness was characterized by clinical evidence of the nephrotic syndrome? Are there glomerular lesions which are histologically diagnostic of certain diseases, such as diabetes mellitus, disseminated lupus erythematosus, eclampsia, or subacute bacterial endocarditis?

These are just a few of the central problems that need to be resolved, with at least some help from a tighter clinicopathologic integration. Not the least of these problems has been the matter of the pathogenetic significance of edema in disorders of the kidneys. Ever since Bright's pioneering realization that "dropsy" and albuminuria were related to renal disease, there has been a lack of agreement on precisely what the relationship was between those cases of nephritis that were predominated by hema-

turia and renal insufficiency and those marked by little more than persistent edema and albuminuria. Volhard and Fahr believed that the edema represented an involvement of tubules ("nephrosis") which could accompany glomerulonephritis as a nephrotic component ("einschlag") or could occur independently as a tubular disease. This point of view is indicated in the classification published in 1914, in their comprehensive monograph which is remarkable for its crystallization of the information then available.

### VOLHARD AND FAHR'S CLASSIFICATION OF BRIGHT'S DISEASE 1914

- I Degenerative diseases—nephroses—with or without amyloidosis of vessels
  - A Acute
  - B Chronic.
  - C Endstage—nephrotic contracted kidney without hypertension
    - Subvariety: necrotizing nephroses
- II Inflammatory diseases—nephritides
  - A Diffuse glomerulonephritis with hypertension
    - 1 acute
    - 2 chronic without insufficiency
    - 3 endstage with insufficiency(All three stages can occur with or without a nephrotic component, that is, with severe and diffuse epithelial degeneration.) (Volhard and Fahr)
  - B Focal nephritides without hypertension
    - 1 Focal glomerulonephritis
      - a acute
      - b chronic.
    - 2 Septic interstitial nephritis
    - 3 Embolic focal nephritis.
- III Arteriosclerotic diseases, sclerosis
  - Benign nephrosclerosis
  - Combination form: malignant contracted kidney—sclerosis plus nephritis)

Because of his belief, shared by many, that "it is not possible to diagnose accurately, during life, the anatomic changes that will be found in the kidney after death," Christian, in 1925, felt justified in proposing a simple classification unencumbered with histologic segregations, and based primarily on the presence or absence of edema

## CHRISTIAN'S CLASSIFICATION OF BRIGHT'S DISEASE

- A Acute nephritis
- B Subacute nephritis
  - 1 Subacute nephritis with edema
  - 2 Hemorrhagic nephritis
- C Chronic nephritis.
  - 1. Chronic nephritis with edema
  - 2 Chronic nephritis without edema
    - Vascular hypertension progressing into nephritis.

Although there are fairly obvious objections to this classification, it did lay stress in an unmistakable manner on at least the clinically different evolution of the disease with and without protracted edema. This mode of thought has recently been given by Ellis, to at least some degree, the kind of sound histologic footing that Christian disavowed. Ellis sharply separates diffuse glomerulonephritis into two groups: type 1 characterized by known preceding infection, hematuria, azotemia, hypertension and a high percentage of recovery, and type 2 ("lipoid nephrosis") with protracted and abundant edema following insidious onset, and recovery in a very few cases. As will be shown, this rigid division into these two types fails to take into account the frequent transition of type 2 into type 1. However, as indicated, Ellis' contribution is his emphasis of the correlation of these clinical types with the histologic changes in the glomeruli.

## CURRENT CLASSIFICATION

Our own observations indicate an even greater pathologic correlation of the forms of glomerulonephritis with, and without, edema. However, there is, in addition, a more or less specific clinicopathologic quality to other varieties of glomerular lesions which, accordingly, would seem to merit incorporation into a classification of glomerular diseases.

In the construction of any classification, the aim, of course, is to achieve a consistent unitarian basis for a systematic arrangement. However, it is often not possible to attain this objective. The reason is obviously that the information available does not permit the comparable categorization of all diseases on the same plane. Therefore, limitations in a

classification arise if some of the diseases are arranged according to etiology, others by their clinical symptoms, and still others by anatomical features. In the schemes used in this text, morphology has been made the dominant key throughout. Where it is required, further definition has been added by compounding the pivotal morphologic disorder with ancillary indications of etiology or duration.

## CLASSIFICATION OF GLOMERULAR DISEASES

## Diffuse

## Acute

- Proliferative
- Exudative
- Necrotizing
- Hemorrhagic
- Membranous (e.g., toxemia of pregnancy)

## Subacute

## Chronic

- Sclerosing
- Membranous (with edema)
- Lobular (with edema)

"lipoid nephrosis"

## Focal

## Inflammatory

## Specific

- "Wire-loop" glomerulonephritis of disseminated lupus erythematosus
- Focal endocarditic glomerulonephritis (so-called "embolic")

## Nonspecific

- Focal non-suppurative glomerulonephritis
- Focal suppurative glomerulonephritis

## Degenerative

- Diabetic glomerulosclerosis
- Amyloidotic glomerulosclerosis
- Argyrosis

## Functional (benign albuminuria)

Diabetic glomerulosclerosis and renal amyloidosis are not generally regarded as glomerular diseases, but their glomerular dominance from both the histologic and functional viewpoints appears to justify a re-consideration of their nature, as will be indicated. However, for purposes of convenience, they will be discussed under "Vascular Diseases," in terms of capillary (albeit glomerular) sclerosis.

## ACUTE DIFFUSE GLOMERULONEPHRITIS

## General Features

## Etiology

Most cases of acute diffuse glomerulonephritis are generally regarded as complications of a current focus of infection or one that has oc-

occurred in the past in any of a number of organs, and has left an altered immunologic status. For example, glomerulonephritis may follow scarlet fever, pneumonia, mastoiditis, osteomyelitis, or bacterial endocarditis. The infection preceding glomerulonephritis is likely to be "deep" in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever (Seegal and Earle). The demonstration of a focus of infection can be established more often in children than in adults, and much less commonly in glomerulonephritis with persistent edema ("lipoid nephrosis") than in "hemorrhagic glomerulonephritis." It is extremely difficult to be certain of the frequency with which glomerulonephritis complicates infections, because, undoubtedly, many of the milder cases are overlooked. Evidence for this conclusion is derived from the fact that, in instances of fatal inflammatory conditions, such as bacterial endocarditis (Bell), ulcerative colitis (Jensen et al.), and rickettsial diseases (Allen and Spitz), a mild, at least histologically demonstrable glomerulonephritis may be found in 50 to 75 per cent of cases. In addition, acute glomerulonephritis may be confused clinically with focal glomerulonephritis which, too, may follow infections. Although the association of nephritis and focal infection is established, there are several predisposing factors, including age and sex, exposure to cold, familial disposition and immunologic status.

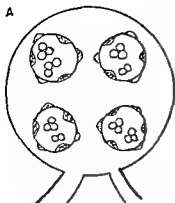
Of the bacteria concerned in the production of glomerulonephritis, the varieties of streptococci play the preponderant role. Infections by the gonococcus, meningococcus, pneumococcus and influenza bacillus are less frequent concomitants of acute diffuse glomerulonephritis. It is of interest that there is no positive relation between the virulence of the streptococci and the occurrence of glomerulonephritis. It is of additional interest in this regard that geographic areas, such as Puerto Rico, may have an incidence of glomerulonephritis equal to that of more northern latitudes, in contrast to the relatively few cases of rheumatic fever in Puerto Rico. Viruses (Herbut) and rickettsias, as indicated, may also be patho-

genetically related to diffuse glomerulonephritis. In this connection, it should be mentioned that acute rheumatic carditis is infrequently associated with acute diffuse glomerulonephritis. On the other hand, chronic rheumatic endocarditis offers no special immunity against glomerulonephritis.

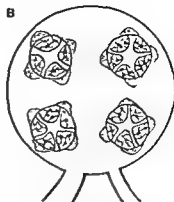
### *Pathogenesis*

The mechanism by which these agents—the bacteria, viruses, and rickettsias—bring about a glomerulonephritis is by no means clear. The bulk of the evidence suggests that they produce glomerular alterations not through their direct action on the glomerular capillaries, but indirectly, probably through the mediation of altered tissue reactivity, hypersensitivity, or some other form of antigen-immune body reactions. The following all point to hypersensitivity as an important factor in the genesis of diffuse glomerulonephritis: the occurrence of glomerulonephritis during convalescence from an infection such as scarlet fever or tonsillitis, rather than at its height, the presence of fairly uniform, diffuse glomerular lesions; the frequent association of glomerulonephritis with outspoken clinical manifestations of serum sickness or allergy, the increased cutaneous reactivity of patients with glomerulonephritis to filtrates of hemolytic streptococci; the development of high antistreptolysin titers; and the experimental evidence based on the use of antikidney serum as well as repeated injections of globulin. In this same connection, it is well to emphasize that the basic phenomena of allergy apply to viruses and rickettsias just as they do to bacteria.

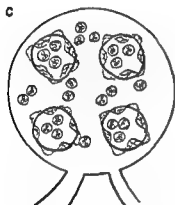
The reactions to the proteid products of bacteria, viruses and rickettsias are not the only means by which glomerulonephritis is caused in the human. We have observed acute diffuse proliferative glomerulonephritis in some instances of chemical poisonings (for example, mercuric chloride) and occasionally following the use of nitrogen mustards in the therapy of cancer. Possibly other allergic mechanisms, in which haptene-like linkages of



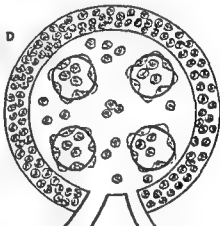
Normal Glomerulus



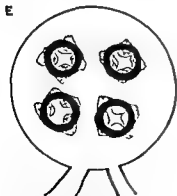
Acute Proliferative  
Glomerulonephritis



Acute Exudative Glomerulo-  
nephritis



Acute Exudative Glomerulo-  
nephritis with Periglomerular  
Lymphangitis



Acute Membranous  
Glomerulonephritis



Acute Necrotizing  
Glomerulonephritis

PLATE 47. ACUTE DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS



FIG. A. Acute diffuse proliferative glomerulonephritis showing marked dilatation of Bowman's space with abundant protein precipitate from permeable only moderately cellular glomerular capillaries. Homogeneous grey-black casts are in distal convoluted tubules with only loose granular precipitate in proximal convoluted tubules (A.F.I.P. Acc. 101695).

FIG. B. Acute diffuse glomeruli from kidney showing disruption of glomerular architecture, fusion of glomerular loops and transuded protein precipitate in Bowman's space. Note too the fibrinoid degeneration of Bowman's capsule.

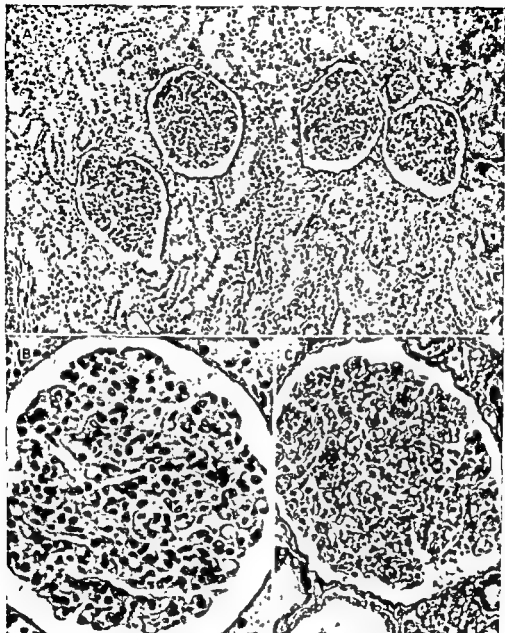


FIG. A. Acute diffuse proliferative glomerulonephritis, characterized by ischemic glomeruli that are larger than normal and have an obviously increased cellularity. The tubules appear uninvolved despite the glomerular ischemia.

FIG. B. Acute diffuse proliferative glomerulonephritis. A higher magnification of a glomerulus from kidney illustrated in figure A. Note the increased numbers of large, hyperchromatic endothelial cells and the moderately swollen capillary basement membrane.

FIG. C. Silver stain of glomerulus from acute diffuse proliferative glomerulonephritis with no significant histologically discernible alteration in the basement membrane. Nevertheless, this patient died of renal insufficiency.



nonbacterial proteins participate, are responsible for some cases of glomerulonephritis in the absence of infection. More recently, it appears that stresses of various sorts with the altered response to corticosteroids potentiated by sodium salts may be another pathogenetic factor in the evolution of glomerulonephritis (Selye).

### *Experimental Glomerulonephritis*

If acute diffuse glomerulonephritis in humans occurs as a result of a hypersensitive reaction to the products of bacteria, rickettsias and viruses, it is a remarkable fact that spontaneous diffuse glomerulonephritis is relatively rare in animals (plate 60). Surely this fact is not dependent on the absence of spontaneous infections in animals. Experimentally, acute diffuse glomerulonephritis has been reported following the injection of bacteria or their products (Duval and Hibbard; Lukens and Longcope), the production of brucellosis (Margolis et al.), the use of foreign proteins (More and Waugh), and the administration of specific antirenal antibodies after the methods of Masugi (Schwentker and Camplow, Smadel; Kay). Of all the procedures used, none has yielded histologic pictures that so closely simulate the spontaneous disease of humans as have the last two methods, the use of repeated injections of gamma globulin and the use of antikidney antibodies. Both of these types of studies suggest an underlying allergic pathogenesis. It is of interest that interference with renal function by unilateral ligation of the ureter tends to inhibit glomerular alteration in the ipsilateral kidney in contrast to the glomerulonephritic changes produced in the opposite kidney by the Masugi procedure (Reubn).

### *Clinical Picture of Acute Diffuse Glomerulonephritis*

Acute diffuse glomerulonephritis may occur at any age, but about 70 per cent begin in the cut example of acute diffuse glomerulonephritis between 5 and 20 years of age. A clear case was reported in a 2 months old infant (Yampolsky and Mullins). Unlike the situation

in chronic pyelonephritis, acute glomerulonephritis is noted about twice as commonly in males as in females. In contrast, the incidence of rheumatic fever is about equal in the two sexes. Occasionally, siblings of families contract the disease almost simultaneously, an occurrence which Addison has regarded as probably signifying a familial predisposition. Whether or not this truly represents some constitutional predisposition or a vulnerability because of similar immunologic behavior, or merely an expected reaction to similar organisms in a similar over all environment, is not clear.

The clinical picture of acute glomerulonephritis may vary from merely the presence of proteinuria as detected in routine examinations, to the full blown clinical picture, including uremia, hypertensive encephalopathy and cardiovascular manifestations; hypertensive neuroretinopathy occurs rarely. The initial phase usually lasts several weeks, but may range from a few days, terminating in resolution or death, to as long as several months.

The signs and symptoms include pallor of the skin, moderate fever, lumbar pain, radiating downward, urgency and frequency of micturition, nocturia, chills, headache, nausea and vomiting, and edema of the eyelids, face and genitalia, as well as of the sacrum in the bedridden. The edema is not the result of generalized capillary damage, but is, on the basis of cardiac failure, and/or osmotic changes in the blood, due to renal damage. The protein content of the edema fluid is comparable to or less than that of edema fluid in cardiac failure (Warren and Stead).

The initial symptoms, especially in children, may be cerebral and may be mistaken for encephalitis. Cardiac insufficiency, some degree of which is present in about 75 per cent of clinically apparent cases, occasionally dominates the clinical picture and may be so striking that the cardiac edema may be erroneously considered of renal origin. Despite the pallor, only a mild degree of anemia is noted, as a rule, in the early stages.

The rise in blood pressure usually affects both the diastolic and systolic levels, but the

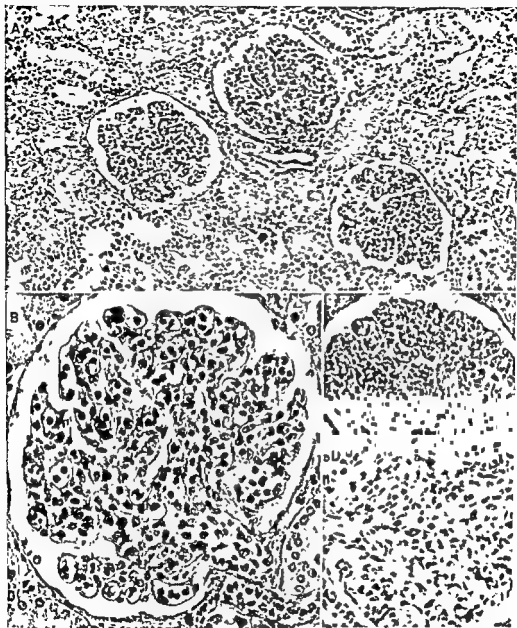
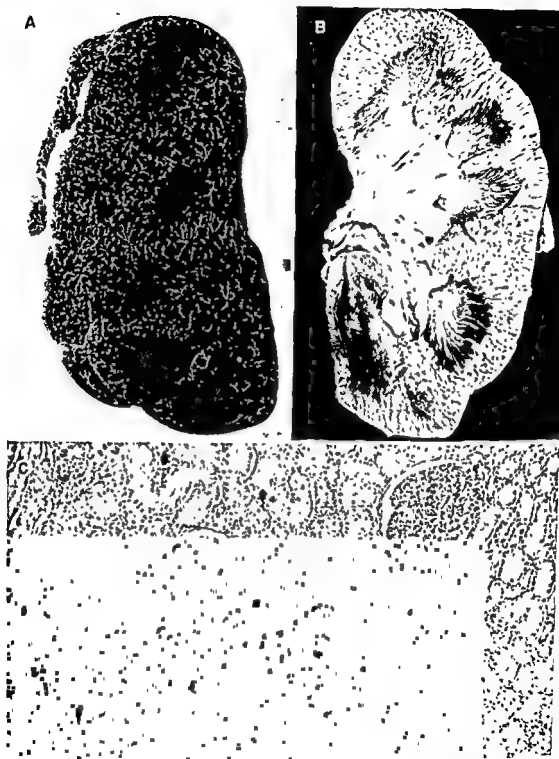


FIG. A. *Acute diffuse exudative glomerulonephritis*. The glomeruli are enlarged, ischemic and excessively cellular. Again, the tubular epithelium is not especially altered, despite the glomerular ischemia.

FIG. B. *Acute diffuse exudative glomerulonephritis*. A higher magnification of glomerulus from kidney of figure A. This is the *exudative* type of glomerulonephritis with polymorphonuclear leukocytes confined in this early stage to the lumens of capillaries.

FIGS. C AND D. *Acute diffuse glomerulonephritis* showing combined features of proliferation and exudation.

# PLATE 50 TRENCH NEPHRITIS



FIGS. A AND B *Trench nephritis* showing the swollen moist cortex and congestion common in banal forms of acute diffuse glomerulonephritis. The surface is mottled by stellate veins (A).

FIG. C *Trench nephritis* with a histological picture of the combined exudative and proliferative types. The glomeruli are considerably enlarged, cellular and ischemic; nevertheless, the tubules are intact, an association that is not uncommon, thereby indicating that serious compromise of the glomeruli need not produce histologically evident tubular alteration.

systolic pressure alone may be elevated, especially at first. In adults, the usual elevation is between 130 and 170 mm, pressures over 200 mm are unusual. In some cases, especially in adults, dyspnea is the prominent symptom and is the result of acute myocardial failure. This was the common picture in trench nephritis, and is a serious prognostic sign, presaging death in the acute stage. Epistaxis, purpura and thrombopenia may also occur.

#### *Laboratory Data*

The urinary volume may be diminished to the point of anuria in the severest cases. The oliguria averages 400 to 600 cc daily and if severe tubular damage is present, the specific gravity of the urine is low and fixed. If the oliguria is due in large measure to cardiac insufficiency, or other prerenal deviation of water such as might occur from vomiting, then the specific gravity is elevated. This feature is of some differential importance in the diagnosis of renal versus extrarenal origin of oliguria, although in practice, it is not nearly so clear cut as it might seem inasmuch as tubular reabsorptive capacity is not diminished in all cases of acute glomerulonephritis.

In acute diffuse glomerulonephritis, the urine practically always contains blood, protein and casts. The hematuria may be evident on gross examination of the urine which appears "smoky," or coffee colored. Actually, as Addison points out, it takes only a drop or two of blood, about 0.2 cc, to produce this discoloration of the urine. The degree of hematuria is not necessarily an indication of the severity or prognosis of the disease. Certainly there is no correlation between the amount of hematuria and the extent of histologically evident glomerular damage. In most cases, hematuria tapers off after a few days or weeks, but a few red blood cells may escape into the urine for months, again without reflection of the prognosis. The erythrocytes may be hemolyzed in their passage through the kidney (plate 55) so that hemoglobinuria may also be present.

As stated, proteinuria is rarely absent in acute diffuse glomerulonephritis. It usually is of the order of 0.3 per cent, but may excep-

tionally exceed 2 per cent. Here, too, the severity of the disease need not parallel the level of albuminuria although if the excretion of albumin is protracted and abundant, the nephrotic syndrome and its attendant perils may be anticipated.

Casts are also almost a constant part of the picture in acute diffuse glomerulonephritis. Early, there are hyaline and epithelial casts predominantly, later, epithelial and granular casts, cylindroids and rarely waxy casts may be added. Polymorphonuclear leukocytes are present in moderate numbers and tubular epithelial cells are found in the later periods. Incidentally, in evaluating the degree of proteinuria, the sediment should be taken into account, for example, 100,000 white blood cells in 2 cc of urine add 0.1 Gm of protein.

The sedimentation rate of the red blood cells is often elevated in acute diffuse glomerulonephritis as are the titers of antistreptolysin and antistreptokinase.

Fatal impairment of renal function in acute diffuse glomerulonephritis does occur but it is a relatively uncommon occurrence. Death, in this acute stage, may result from cardiac failure. Oftentimes, as a result of prerenal deviation of fluid, there is a disparity between the minor degree of renal impairment and the marked azotemia in acute glomerulonephritis. In such cases, the phenolsulphonphthalein test may show an excretion of somewhere around 10 per cent in two hours, despite the lack of appreciable renal dysfunction.

#### *Clinical Evolution of Acute Diffuse Glomerulonephritis*

The answer to the question, "What percentage of patients with acute diffuse glomerulonephritis recovers completely?" depends on whether the clinically evident or the histologically evident disease is meant. As has already been stated, in a variety of infections, or, at least, inflammatory diseases, histologically documentable acute diffuse glomerulonephritis occurs in from 50 to 75 per cent of patients. These lesions are of the exudative and/or proliferative types, rarely of the necrotizing

PLATE 50. TRENCH NEPHRITIS



FIGS A AND B *Trench nephritis* showing the swollen moist cortex and congestion common in banal forms of acute diffuse glomerulonephritis. The surface is mottled by stellate veins(A)

FIG C *Trench nephritis* with a histological picture of the combined exudative and proliferative types. The glomeruli are considerably enlarged, cellular and ischemic, nevertheless, the tubules are intact, an association that is not uncommon, thereby indicating that serious compromise of the glomeruli need not produce histologically evident tubular alteration

systolic pressure alone may be elevated, especially at first. In adults, the usual elevation is between 130 and 170 mm, pressures over 200 mm are unusual. In some cases, especially in adults, dyspnea is the prominent symptom and is the result of acute myocardial failure. This was the common picture in trench nephritis, and is a serious prognostic sign, presaging death in the acute stage. Epistaxis, purpura and thrombopenia may also occur.

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PLATE 51. TRENCH NEPHRITIS

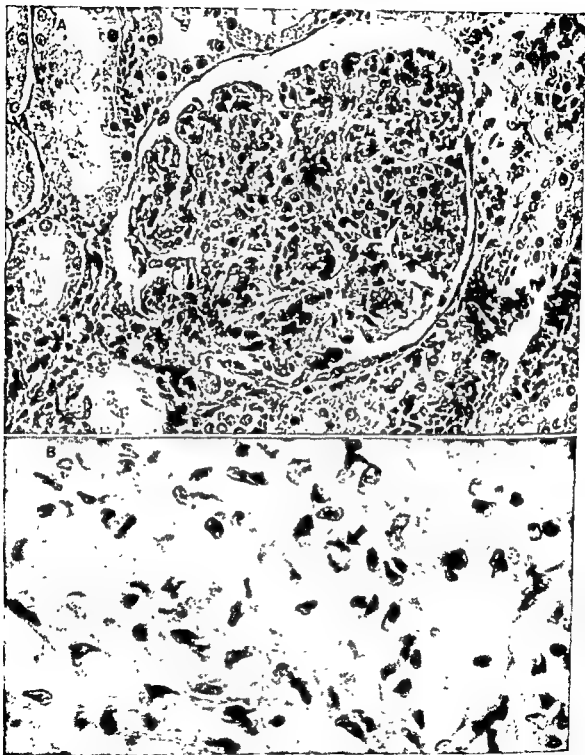


FIG A *Trench nephritis* characterized by acute diffuse proliferative and exudative glomerulonephritis

FIG B *Mitotic figure* (arrow) in endothelial cell of glomerulus of acute diffuse glomerulonephritis in *trench nephritis*



FIG A Exudative type of acute diffuse glomerulonephritis produced in this case by toxicity to sulfathiazole and characterized by polymorphonuclear leukocytes in glomerular capillaries, Bowman's space and periglomerular lymphatics (Compare plate 46D)

FIG B Exudative and proliferative type of acute diffuse glomerulonephritis Note exudation of polymorphonuclear leukocytes, proliferation of endothelial cells and ischemia



type. Therefore it would be expected that if the patient had recovered from the primary illness—for example, subacute bacterial endocarditis, typhus fever, or ulcerative colitis—then, with few exceptions, the glomerulonephritis would have healed. In most of these cases, the glomerulonephritis is not recognized clinically, although, in retrospect, there is usually adequate basis for the diagnosis. Hence, to return to the original question, if such less overt forms of glomerulonephritis are included in the

sample, it is of further interest to learn that of all the glomerulonephritic patients seen at Addis' clinic, 52 per cent died of their renal disease, and 48 per cent recovered. These are patients who were referred to the clinic at various stages of their disease. Many of the patients were already "on their way to death" when first seen, so that, again, the number of fatalities is large. The course of acute diffuse glomerulonephritis as represented by Addis is shown in figure 1.

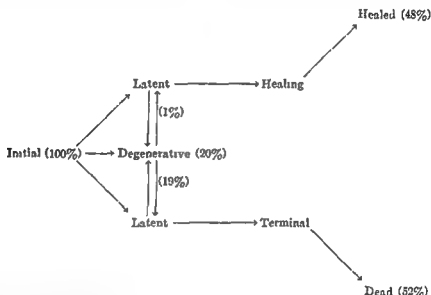


Fig 1. Course of Clinically Evident Acute Glomerulonephritis (From Addis: *Glomerular Nephritis*, New York, The Macmillan Co., 1948)

sample, the answer is that a very small percentage—perhaps several per cent—of cases of acute diffuse glomerulonephritis die of renal failure.

On the other hand, of those patients with acute diffuse glomerulonephritis who are seen in the acute stage at a nephritis clinic, fully 20 per cent expire as a direct result of the renal insufficiency, and the remainder, 80 per cent, recover from the renal disease (Addis). However, these are patients who have been referred to a famous clinic for kidney disorders, so that it is obvious, as Addis notes, that the statistical sample is not representative of the over-all "nephritic population." The percentage of recoveries in the latter group would undoubtedly be greater than 80 per cent. Despite the acknowledged selectivity of the

According to the definitions of Addis, the initial phase is characterized by coffee-colored urine, edema and hypertension; the latent stage, beginning within a month after the onset of the disease, is identified merely by an abnormal urinary sediment; the degenerative stage is the clinical nephrotic syndrome.

Exceptionally, as indicated, death occurs from renal failure during the acute stage of the disease (plates 47-55). As a rule, the patient recovers. Of 88 such healed cases, 81.8 per cent recovered within two years, 5.7 per cent took 6 to 10 years (Addis). In the minority of cases, then, there is evolved the picture of subacute or chronic glomerulonephritis after more or less of a latent stage in some instances. Cases of apparently completely healed acute diffuse glomerulonephritis rarely relapse. The chronic

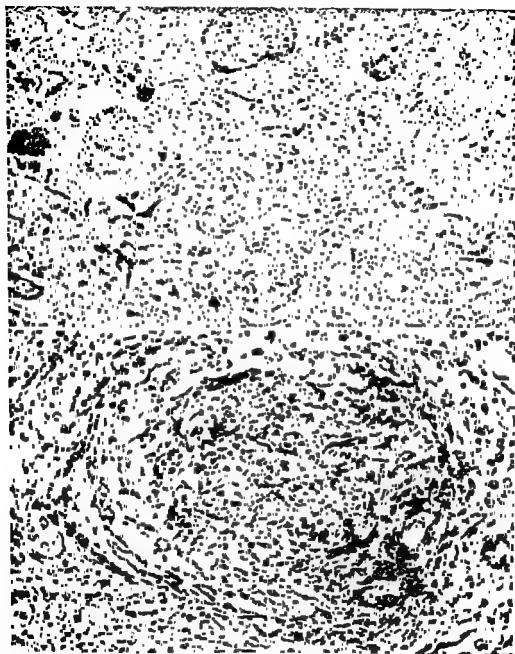


FIG. 1. Necrotizing type of acute diffuse glomerulonephritis characterized by exudation of polymorphonuclear leukocytes, disruption of glomerular architecture, glomerular ischemia and fibrinoid necrosis of capillary walls. Note blood in distal tubules.

FIG. 2. Exudation, fibrinoid degeneration and thrombosis of glomerular capillaries in acute diffuse necrotizing glomerulonephritis. It is clear that such garbled glomeruli cannot be restored to normal, unlike those of proliferative or exudative glomerulonephritis.

PLATE 54. ACUTE DIFFUSE HEMORRHAGIC GLOMERULONEPHRITIS

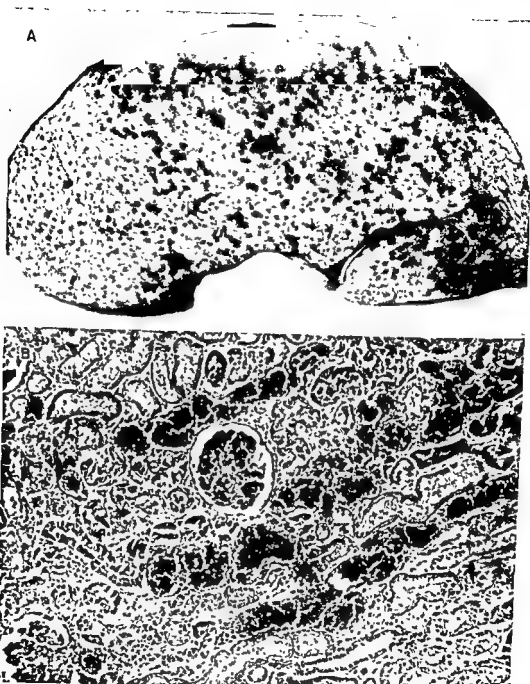


FIG A *Acute diffuse hemorrhagic glomerulonephritis* showing the numerous cortical flecks of blood corresponding to the blood in the tubules as shown in figure B. Grossly, this kidney also resembles that of focal endocarditic glomerulonephritis (plate 85A) and malignant nephrosclerosis (plate 211A).

FIG B This photomicrograph is of a section taken from kidney illustrated in figure A. Masses of red blood cells are in the distal nephron. The proximal nephrons are free of blood. The representative glomerulus illustrates the thromboses characterizing this lesion and the relatively minimal additional glomerular alteration that is often present in this variety of glomerulonephritis (further shown in plate 55A).

phase may be a continuous and rapid progression of the acute stage with death in uremia in a few weeks or months, or there may be a variable dormant period with inconstant amounts of slight to moderate proteinuria as the only manifestation of the disease. This type may remain latent or finally develop one or other of the clinical variants of chronic glomerulonephritis to be described in the section on that topic. Another group may escape the acute phase merely with hypertension. Some cases actually develop the phase of accelerated or malignant hypertension. Still others, the recurrent type, develop repeated acute attacks of glomerulonephritis, usually followed eventually by renal insufficiency.

Finally, there is yet another, prognostically grave group which is predominated by a persistent abundant albuminuria and edema, although infrequently this type may be initiated with the signs of a hemorrhagic glomerulonephritis (Schwarz et al.). In many of these instances, the fatal termination is the result of secondary infection, in some, there is ultimate progression to hypertension and renal insufficiency. This is the hitherto controversial category of cases which has in the past been called "lipoid nephrosis," but for etiopathologic reasons to be outlined, clearly appears to be a variant of diffuse glomerulonephritis, either of the membranous or lobular types (plates 73-80).

#### *Prognostic Factors*

There is no way of making certain what the outcome of an attack of acute diffuse glomerulonephritis will be. There is suggestive evidence that adequate therapy with penicillin early in the course of the disease—that is, within the first days—reduces the severity (but not the incidence) of glomerulonephritis and its sequelae (Weinstein et al.). Certain data, however, do furnish presumptive prognostic clues. The clinical severity of the initial attack is not necessarily an indication of the future tempo of evolution of the disease. In some of the severest cases, recovery has occurred within the first year. However, the presence of hypertension and renal impairment for more than a few months after the onset, makes complete

recovery highly unlikely. In those cases with marked albuminuria and edema, the additional feature of hypertension adds a serious increment to the gravity of the prognosis. In general, the prognosis varies with the height of the blood pressure, especially the diastolic pressure. Hypertensive neuroretinopathy, epileptiform convulsions and other signs of hypertensive encephalopathy are ominous. Another guide to the progress of the condition is the trend in the capacity to concentrate the urine. The specific gravity, even of routine morning specimens of urine over a period of weeks or months is likely to reflect the deterioration of the kidney by the trend of progressive lowering of the specific gravity. In the absence of any indication of progression of the disease, even though hypertension, proteinuria and some edema may exist, the capacity to live normal lives may be retained for years. However, such patients remain vulnerable to sudden relapse from intercurrent infection, cardiac failure or pregnancy.

#### GENERAL FEATURES OF PATHOLOGY OF ACUTE DIFFUSE GLOMERULONEPHRITIS

##### *Gross Appearance*

In the very early or mild cases, there may be no demonstrable gross changes. As a rule, however, the kidneys are enlarged from one and one-half to twice normal size. The capsules may be stripped easily, disclosing a smooth surface which is deep purplish-brown or a pale greyish-brown, depending on the state of congestion (plates 50 A, B). The surface is usually reddish, smooth and may be dotted with fine punctate hemorrhages. The cut surface may be pale yellowish-grey, but is often moist and deep red. The cortex and medulla are fairly sharply differentiated. The pyramids are markedly congested and because of the red streaks of hyperemic vasa recta may grossly simulate a hemoglobinuric nephrosis, indeed, blood or hemoglobin may actually be present in the tubules, so as to add to the red radial striae. On careful examination with the naked eye, the glomeruli characteristically are more prominent than normally and are visible as fine, whitish dots—whitish because of the ischemia and cellular

PLATE 55. ACUTE DIFFUSE HEMORRHAGIC GLOMERULONEPHRITIS



FIG A In this instance, there is acute proliferative glomerulitis with red blood cells principally in the proximal nephron, no blood is present in Bowman's space

FIG B Acute diffuse hemorrhagic glomerulonephritis from the same case illustrated in figure A. Red blood cells and hemoglobin (from laked tubular blood) are present in the distal tubules, and may be mistaken for hemoglobinuria (lower nephron) nephrosis



FIG. A *Hydropic vacuolated epithelium of proximal convoluted tubules in acute diffuse proliferative and exudative glomerulonephritis. This vacuolated change is attributed to changes in oncotic pressure very much as in hypertonic sucrose nephrosis in which the epithelial change is identical*

FIG. B *Proximal tubular epithelial necrosis and regeneration in acute diffuse proliferative glomerulonephritis*

FIG. C *Flattened, elongated, hyperchromatic, regenerating epithelial cell (arrow) of proximal tubule in acute proliferative glomerulonephritis*

proliferation. However, in some instances they are distinctly red because of intraglomerular hemorrhages or congestion, in still others, they may be hidden from view by swollen adjacent parenchyma.

### *Histologic Appearance*

#### *Glomeruli*

The histologic changes of acute diffuse glomerulonephritis do not conform to a single standard prototype. The picture varies considerably. The pathogenetic basis for the variable histologic response is obscure, but it would seem likely that these morphologic alterations are an expression of the degree of the allerg-immunologic reaction rather than of the difference in the various provocative agents. These agents may be drugs, bacteria, rickettsias, viruses or their antigenic products, the histologic effects of which are modified by the state of reactivity of the renal tissue.

The changes are essentially a diffuse glomerular capillaritis. The inflammation of the loops may take the form of swelling, hyperchromatism and proliferation of the fixed cellular elements, thickening, reduplication and granular fibrinoid alteration of the capillary basement membrane with or without glomerular thromboses, the accumulation of polymorphonuclear leukocytes, both intra- and extravascularly, gnarled distortion of the glomerular capillaries, and finally, a combination of any of these changes.

From the functional viewpoint, the most important histologically visible result is glomerular ischemia and evidence of interference with glomerular blood flow and glomerular filtration. Less obvious changes leading to abnormal permeability of the glomerular capillaries may occur. In many cases, the degree of altered glomerular permeability is not apparent from the histologic sections, but in the membranous and lobular glomerulonephritis to be described, a mere examination of the sections yields this information (plates 73-80).

#### *Tubules*

The physiologic evaluation of the tubular change in acute diffuse glomerulonephritis is an exceedingly difficult problem. Contrary to

what might be anticipated, there is no direct correlation between the degree of glomerular and tubular changes, even though it is generally assumed that the tubular damage is secondary to the compromise of their blood supply by glomerular ischemia. Actually, the epithelium of the tubules may be histologically unaltered, notwithstanding acute glomerular change, so that the concentrating ability of the kidney is unimpaired. On the other hand, the tubular epithelium, particularly that of the proximal nephron, may be vacuolated with lipid or fluid (plates 56, 66), may contain huge hyaline granules (plate 75 C), or may be so necrotic as to suggest a primary necrotizing tubular disease (plate 56 B, C). The variable extent of this damage is the reason for the variable tubular function in glomerulonephritis, especially as revealed by the specific gravity of the urine.

The individual histologic forms of glomerulonephritis (plate 46) are considered in the following sections.

### ACUTE DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS

Acute proliferative glomerulonephritis is characterized by diffuse involvement of glomeruli with hyperplasia and swelling principally of the endothelial cells and to a lesser extent of the epithelial cells (plates 47, 48). The increase in size of the individual cells involves the nuclei particularly. The lumens of the glomerular capillaries tend to be ischemic. The basement membrane typically is histologically unaltered, in this form, although some observers require that the basement membrane be altered before the diagnosis of glomerulonephritis is made. Bowman's space tends to be narrowed by the enlarged malpighian tufts, Bowman's capsule is usually unchanged, but occasionally shows a segmental fibrinoid swelling (plate 169 B). The extraglomerular vessels are not remarkable. As a rule, there is no associated interstitial inflammation. Isolated hemoglobin casts may be found in loops of the distal convoluted tubules situated near the glomerulus; the medullary tubules are spared. The epithelium of the tubules shows no changes of note although sometimes the epithelium of the

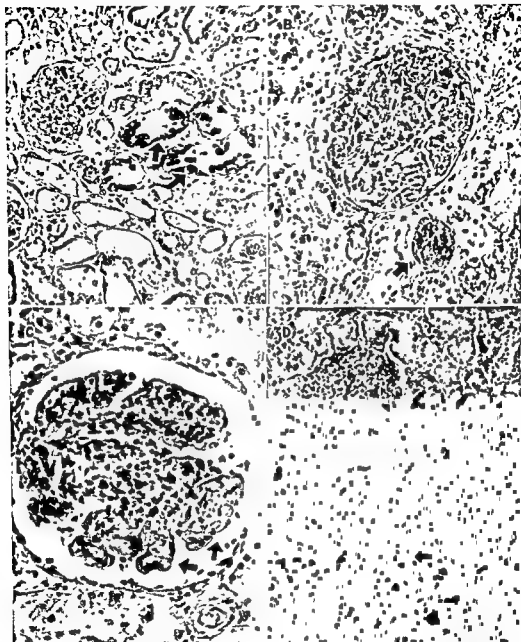


FIG A Acute diffuse proliferative glomerulonephritis attributed to a nitrogen mustard (SK1195). The dark luminal masses (arrows) represent calcification of necrotic epithelium of proximal tubules.

FIG C Acute diffuse proliferative glomerulonephritis with focal fibrinoid swelling of glomerular capillaries (arrows) similar to the "wire-loop" changes of disseminated lupus erythematosus. No other stigmata of lupus erythematosus were present.

FIG B Acute diffuse necrotizing glomerulonephritis in a patient with fulminant influenzal type of interstitial pneumonitis, associated with marked hematuria. A blood cast is seen in a distal convoluted tubule (arrow).

FIG D Nonspecific acute diffuse exudative and proliferative glomerulonephritis associated with blastomycotic nephritis. Blastomycetes (arrow).



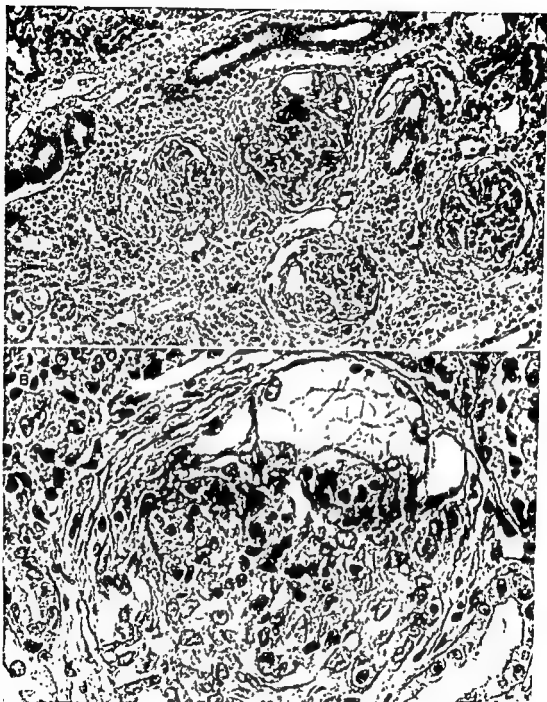


FIG A *Experimental chronic sclerosing glomerulonephritis* produced in rabbits by the injection of bovine serum gamma globulin after unilateral nephrectomy

FIG B *Glomerular alteration* from case of experimental glomerulonephritis illustrated above. The crescent, glomerular ischemia, fusion and thickening of capillaries, proteid exudation and the cellular proliferation make this picture indistinguishable from the lesion of human chronic glomerulonephritis (Histologic slides obtained through the courtesy of Dr. R. H. More)

proximal tubules may show hydropic vacuolization

This form of glomerulonephritis occurs commonly in a variety of infectious and allergic diseases and may be undetected clinically. In view of the retention of basic architecture, it is a reversible type of glomerulonephritis in its early stage, and commonly is completely resolved if the underlying primary disease is cleared.

#### ACUTE DIFFUSE EXUDATIVE GLOMERULONEPHRITIS

Acute diffuse exudative glomerulonephritis also involves all of the glomeruli and the essential feature is the presence of polymorphonuclear leukocytes within the lumens of the ischemic glomerular capillaries (plate 49). Because the leukocytes are practically confined to the capillary lumens and spare Bowman's space, the lesion may be overlooked and the leukocytes regarded merely as a reflection of their preponderance in the peripheral blood. The leukocytes within the glomeruli may be the only visible change, although not infrequently the exudative glomerulonephritis may be associated with features of the proliferative form, particularly the swelling and hyperplasia of the endothelial cells (plates 49 C, D and 50), changes in the basement membrane and adhesions between loops are usually absent. In extreme cases, the exudate of polymorphonuclear neutrophils may fill not only the lumens of the glomerular capillaries but also Bowman's space and the surrounding periglomerular lymphatic channels (plate 52 A). This type, too, is reversible in its early stage.

#### ACUTE DIFFUSE NECROTIZING GLOMERULONEPHRITIS

In acute necrotizing glomerulonephritis, there is diffuse involvement of glomeruli characterized by ischemia, patchy, fibrinoid degeneration of glomerular capillary walls, necrosis as well as irregular proliferation of epithelial and endothelial cells, and focal capillary thromboses (plate 53). The fibrinoid alteration may involve also Bowman's capsule and the afferent arterioles. The efferent arterioles seem to be spared. There may be considerable associated

interstitial edema and focal infiltrations of lymphocytes, plasma cells and histiocytes. The epithelium of the proximal convoluted tubules may show more or less degeneration beyond the stage of so-called cloudy swelling and may be accompanied by evidence of epithelial regeneration. Loose granular protein precipitate often with intact or partially laked and fragmented red blood cells may be found in Bowman's space and in the lumen of the proximal part of the nephron. The distal nephron may contain hyaline acidophilic casts, and red blood cells in various stages of degeneration, either loose or in casts. All in all, there is generally a marked disparity between the relatively slight tubular changes and the striking glomerular destruction. The prognosis for this type is most serious.

#### ACUTE DIFFUSE HEMORRHAGIC GLOMERULONEPHRITIS

In the kidney of acute diffuse hemorrhagic glomerulonephritis, the most evident change is the presence of large numbers of intact red blood cells dilating Bowman's space and thereafter filling the proximal convoluted tubules. Occasionally, the red blood cells are altogether absent from the proximal nephron and are first seen in the more distal portions of the nephron. In this location, the blood may have been altered into casts of hemoglobin, and on this basis, the lesion confused with hemoglobinuric or lower nephron nephrosis (plates 54, 55). Except for the slight to moderate swelling and proliferation of endothelial cells, the glomeruli may show remarkably little alteration despite the obvious evidence that there has been permeability to red blood cells.

#### ACUTE MEMBRANOUS GLOMERULONEPHRITIS

Acute diffuse membranous glomerulonephritis occurs not only in eclampsia, but as the first stage of the chronic membranous glomerulonephritis with edema ("hypoid nephrosis," type 2 of Ellis), and as the stage preceding the late or contracted phase of many of the cases of sclerotic glomerulonephritis that were earlier characterized by abundant edema. In eclampsia, the clinical picture is modified by the gestation, although edema, albuminuria,

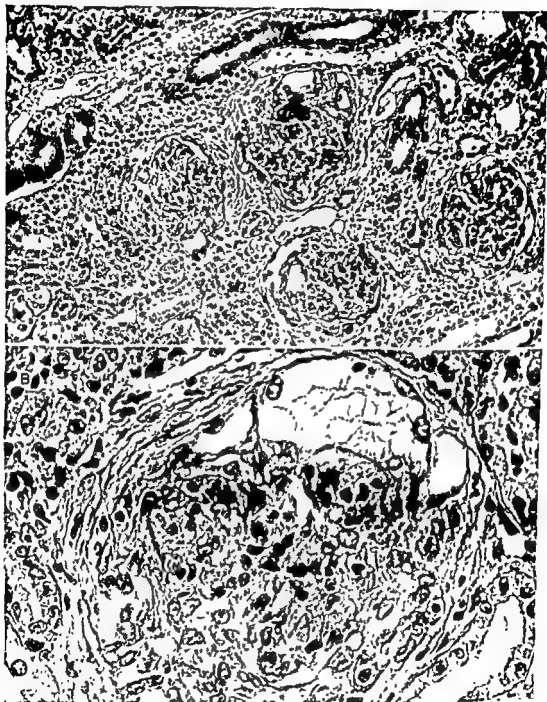


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proximal tubules may show hydropic vacuolization.

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PLATE 58. EXPERIMENTAL CHRONIC DIFFUSE GLOMERULONEPHRITIS

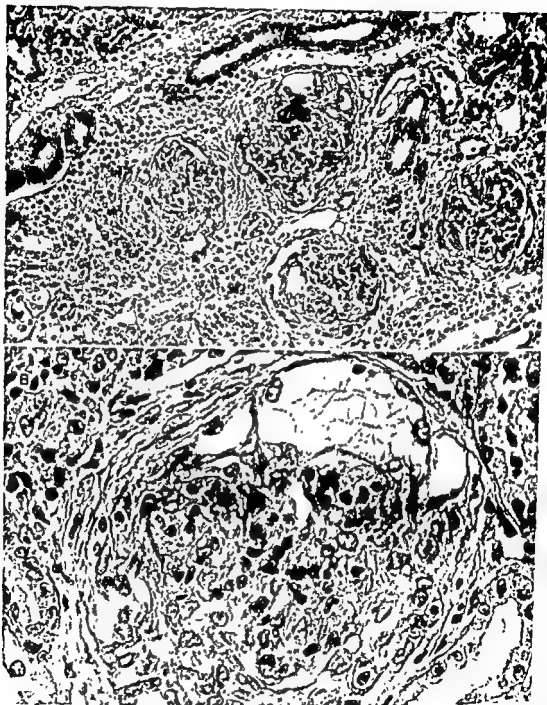


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Acute diffuse exudative glomerulonephritis also involves all of the glomeruli and the essential feature is the presence of polymorphonuclear leukocytes within the lumens of the ischemic glomerular capillaries (plate 49). Because the leukocytes are practically confined to the capillary lumens and spare Bowman's space, the lesion may be overlooked and the leukocytes regarded merely as a reflection of their preponderance in the peripheral blood. The leukocytes within the glomeruli may be the only visible change, although not infrequently the exudative glomerulonephritis may be associated with features of the proliferative form, particularly the swelling and hyperplasia of the endothelial cells (plates 49 C, D and 50), changes in the basement membrane and adhesions between loops are usually absent. In extreme cases, the exudate of polymorphonuclear neutrophils may fill not only the lumens of the glomerular capillaries but also Bowman's space and the surrounding periglomerular lymphatic channels (plate 52 A). This type, too, is reversible in its early stage.

#### ACUTE DIFFUSE NECROTIZING GLOMERULONEPHRITIS

In acute necrotizing glomerulonephritis, there is diffuse involvement of glomeruli characterized by ischemia, patchy, fibrinoid degeneration of glomerular capillary walls, necrosis as well as irregular proliferation of epithelial and endothelial cells, and focal capillary thromboses (plate 53). The fibrinoid alteration may involve also Bowman's capsule and the afferent arterioles. The efferent arterioles seem to be spared. There may be considerable associated

interstitial edema and focal infiltrations of lymphocytes, plasma cells and histiocytes. The epithelium of the proximal convoluted tubules may show more or less degeneration beyond the stage of so-called cloudy swelling and may be accompanied by evidence of epithelial regeneration. Loose granular protein precipitate often with intact or partially laked and fragmented red blood cells may be found in Bowman's space and in the lumen of the proximal part of the nephron. The distal nephron may contain hyaline acidophilic casts, and red blood cells in various stages of degeneration, either loose or in casts. All in all, there is generally a marked disparity between the relatively slight tubular changes and the striking glomerular destruction. The prognosis for this type is most serious.

#### ACUTE DIFFUSE HEMORRHAGIC GLOMERULONEPHRITIS

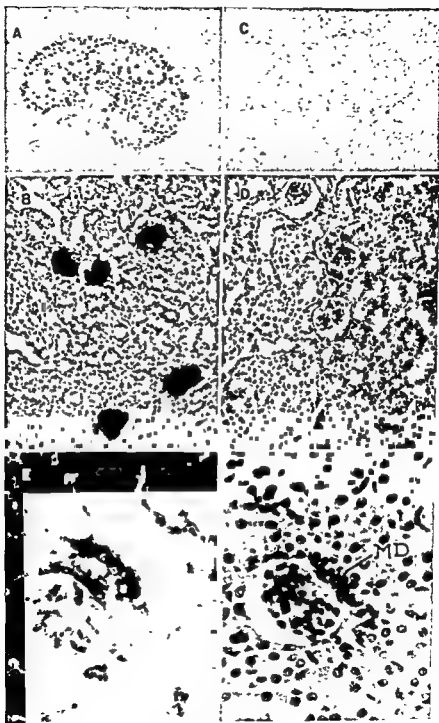
In the kidney of acute diffuse hemorrhagic glomerulonephritis, the most evident change is the presence of large numbers of intact red blood cells dilating Bowman's space and therefore filling the proximal convoluted tubules. Occasionally, the red blood cells are altogether absent from the proximal nephron and are first seen in the more distal portions of the nephron. In this location, the blood may have been altered into casts of hemoglobin, and on this basis, the lesion confused with hemoglobinuric or lower nephron nephrosis (plates 54,

despite the obvious evidence that there has been permeability to red blood cells).

#### ACUTE MEMBRANOUS GLOMERULONEPHRITIS

Acute diffuse membranous glomerulonephritis occurs not only in eclampsia, but as the first stage of the chronic membranous glomerulonephritis with edema ("lipoid nephrosis," type 2 of Ellis), and as the stage preceding the late or contracted phase of many of the cases of sclerotic glomerulonephritis that were earlier characterized by abundant edema. In eclampsia, the clinical picture is modified by the gestation, although edema, albuminuria,

PLATE 59. RENAL LOCALIZATION OF ANTIBODIES



(Legends on facing page)

and hypoproteinemia, here too, are often a prominent part of the syndrome, as would be anticipated. It appears also likely that the lesion of syphilitic nephrosis is an acute, reversible membranous glomerulonephritis, although the available data do not permit a documented statement on this subject.

### *Histology*

The lesion of acute membranous glomerulonephritis is characterized by a soft fibrinoid swelling of the walls of the glomerular capillaries (plate 101). Usually this swelling is quite uniform and diffuse and may be associated with slight to moderate proliferation and swelling, particularly of the glomerular endothelial cells. The lumens of the glomerular capillaries are ischemic and may contain fibrinous thrombi. In many instances there is evidence of a markedly increased permeability of the glomerular capillaries to protein as manifested by the proteid fluid in Bowman's space, at times so abundant as to compress the tuft. In addition, the degenerative and regenerative alterations of the epithelium of the proximal convoluted tubules may be so marked as to be confused with a primary necrotizing tubular disease. It is remarkable that in acute diffuse membranous glomerulonephritis red blood cells are rarely seen in Bowman's space or in the tubules, in contrast to the situation in acute diffuse hemorrhagic glomerulonephritis, notwithstanding the far greater histologic change in the glomerular capillary basement membranes in the former.

### **SUBACUTE DIFFUSE GLOMERULONEPHRITIS**

The designation of "subacute" glomerulonephritis is an arbitrary clinical reference to the disease which has lasted from about three to

twelve months. There is questionable nosologic justification for this separate intermediate group, but the histologic changes in the kidneys in these cases are of interest not only because of certain distinctive features, but also in terms of the evolution of the lesions in the more protracted or chronic cases. The patients with subacute glomerulonephritis tend to have abundant albuminuria, often in association with edema, hypoproteinemia, hypercholesterolemia, moderate hypertension and anemia. Terminal renal insufficiency with oliguria and urine of low specific gravity because of the tubular damage are the rule.

### *Pathologic Anatomy of Subacute Diffuse Glomerulonephritis*

The kidneys of subacute diffuse glomerulonephritis are not contracted, but are usually larger than normal and have pale or greyish-yellow smooth surfaces. Many are grossly quite like those of so-called "lipoid nephrosis", the reasons for this are understandable in view of the clinical picture. Subacute glomerulonephritis, therefore, is what was formerly called the "large white kidney," in contrast to the "small white kidney" of the third or chronic stage of glomerulonephritis, and in contrast to the "red" kidneys of arteriolar nephrosclerosis. Other names are still occasionally retained to signify subacute glomerulonephritis, these names include subchronic nephritis, glomerulotubular nephritis and diffuse parenchymatous nephritis.

### *Histologic Types of Subacute Diffuse Glomerulonephritis*

Histologically three essential patterns of glomerular change occur although it appears

**FIGS. A AND B.** Radioautographs of kidneys of a mouse injected with radio-anti-mouse-kidney serum showing a selective concentration of radioactivity in the glomeruli. (Exposure on Ansco No screen x ray film.)

**FIGS. C AND D.** Control radioautographs of the entire kidney and a histologic section from a mouse which received radio anti mouse kidney serum. There is no evidence of significant radioactivity. (Courtesy of H. Pressman, see Science 102: 65-66, 49, J. Immunol. 64: 284-287, 1950.)

**FIGS. E AND F.** Fluorescein labeled antiserum against H. Friedlander. The section (E and F) is from the kidney of a mouse given an intravenous injection of capsular polysaccharide of H. Friedlander 48 hours before being sacrificed. The histologic section, itself, was then treated with the fluorescent antibody and the same field photographed under the fluorescent microscope (E) as well as with visible light (F). The antibody appears concentrated in the macula densa (MD). (Courtesy of Hill, A. G. S., Deane, H. W., and Coons, A. H. J. Exper. Med. 92: 35-41, 1950.)



PLATE 60 CHRONIC SCLEROSING AND MEMBRANOUS GLOMERULONEPHRITIS  
OF DOG



FIG A Spontaneous chronic sclerosing glomerulonephritis of dog showing diffuse glomerular as well as tubular change. The glomerular capillaries are focally scarred but some have walls with diffuse membranous thickening. The epithelium of the proximal convoluted tubules is vacuolated by fat as in human cases of chronic nephrotic glomerulonephritis.

FIG B Markedly scarred glomerulus from case illustrated above.

FIG C Two glomeruli, one with its capillaries practically obliterated, the other with focal fibrosis

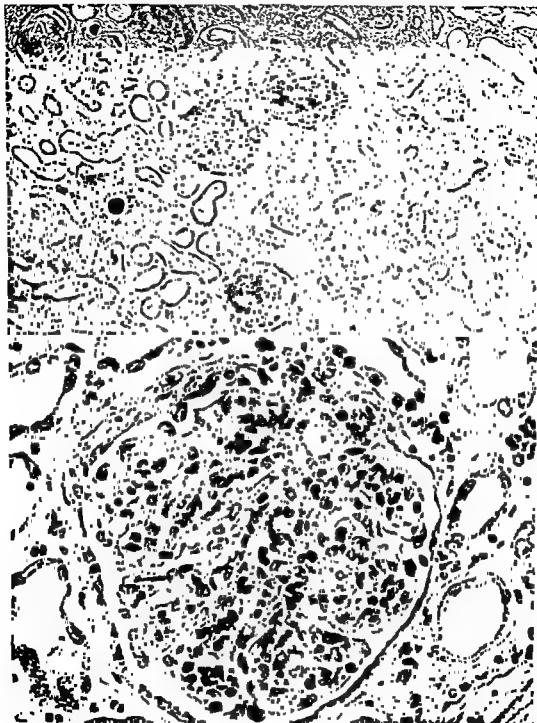


FIG. A Subacute diffuse glomerulonephritis showing crescents, proliferative glomerulitis, focal interstitial inflammation with fibrosis, and exudate in tubular lumens

FIG. B Early crescent formation in subacute diffuse glomerulonephritis showing proliferative glomerulitis. The focus of early crescent formation is characterized by fibrinoid swelling of Bowman's capsule and swelling and proliferation of the epithelial cells. Interstitial edema is also seen

PLATE 62. SUBACUTE DIFFUSE GLOMERULONEPHRITIS



FIG A Red blood cells and casts in distal tubules in a case of subacute diffuse glomerulonephritis

FIG C Crescent of subacute glomerulonephritis made up of proliferating epithelial cells some of which have become elongated to form fibroblasts

FIG B Fibrin and proteoid fluid form a basis for a milieu in which proliferating cells may form a crescent

FIG D Crescent of epithelial cells in the proteoid fluid in Bowman's space

FIG E Fibrinoid degeneration of interlobular artery in subacute diffuse glomerulonephritis.

generally to be taught that, by definition, the microscopic representation of subacute diffuse glomerulonephritis consists of glomerular crescents. The three types include (1) the crescentic form (so-called extracapillary glomerulonephritis), (2) the proliferative form (so-called intracapillary glomerulonephritis, in which no crescents are present) and (3) the membranous form.

### *Crescentic type*

The crescents of subacute diffuse glomerulonephritis occupy more or less of a segment of Bowman's space and are bounded by Bowman's capsule on the convexity (plates 61-63). The concave surface may be free in Bowman's space or may be fused with the periphery of the glomerular capillaries. They are generally considered to be of two types: the *epithelial* and the *fibrous*; actually they are probably of the same genesis, differing only in degree of development.

Epithelial cells, either from the visceral or parietal layers of Bowman's capsule, or from both layers, proliferate within a protein fluid circulated in Bowman's spaces. The impression is gained that these epithelial cells, in such a medium become spindle-shaped and tapered so as to be morphologically and apparently functionally indistinguishable from fibroblasts. White blood cells, including migrating monocytes, may contribute to the crescent and its organization. The thought of epithelial cells transforming into fibroblasts may be unacceptable to those who adhere inflexibly to the absolute specificity of germ layers, but there is an increasing bulk of evidence supporting the thesis that the rigid specificity of germ layers is violated under certain conditions. For example, the formation of cartilage in which epithelium plays the role of chondrocytes is a commonly observed experience in the so-called mixed tumors of salivary, lacrimal, sweat and mammary glands (Allen).

The end result of the crescent is a fibrous demilune either separated from the malpighian tuft or imperceptibly incorporated within it. The degree of fibrosis of the crescent is usually similar to that of the tuft, but may be more or less advanced (plate 63). At times, the crescent is honeycombed into a so-called adenomatoid formation (plate 63 C). The fibrotic crescent

is indicative of a long-standing process such as occurs uniformly in chronic glomerulonephritis. However, crescents, recent or old, are not specific for glomerulonephritis, inasmuch as identical formations may occur particularly in glomeruli in cases of arteriolar, especially malignant, nephrosclerosis, as well as in chronic pyelonephritis, apparently in response to ischemia due to arteriolar narrowing (plate 218 A). In the latter conditions, however, the crescents are confined to a few isolated glomeruli, whereas in subacute glomerulonephritis, they are more or less diffuse.

As a rule the malpighian tuft itself shows the lesion of proliferative or membranous glomerulonephritis. In other words, there is generally glomerular ischemia associated with endothelial cell hyperplasia and thickening of the basement membrane. As a result of the glomerular ischemia, there are varying degrees of tubular atrophy, interstitial fibrosis and focal interstitial inflammation. The extraglomerular vessels are usually spared but occasionally the afferent arterioles, particularly, are thickened. It should be noted finally that while widespread glomerular crescents are generally indicative of a process of subacute duration, there are instances of acute glomerulonephritis in which crescents appear to have been formed within three weeks (plate 64).

## CHRONIC GLOMERULONEPHRITIS

### *Clinical Picture*

The clinical picture of chronic glomerulonephritis is dependent upon and is therefore naturally as variegated as the histologic features of the nephritic kidney. Any one sign or symptom, or combination of them, may characterize an individual case. It is a remarkable fact that not infrequently the kidneys may be severely damaged before the patient or even the physician is aware of the disease. Proteinuria or hypertension may be the initial unsuspected finding of chronic glomerulonephritis in an apparently healthy person undergoing a routine physical examination. The true onset of the nephritis, if it was ever apparent, will very often have been forgotten, overlooked or misinterpreted and the patient will present himself in the late stages with easily correlated symp-

PLATE 63. SUBACUTE DIFFUSE GLOMERULONEPHRITIS: EVOLUTION OF CRESCENTS

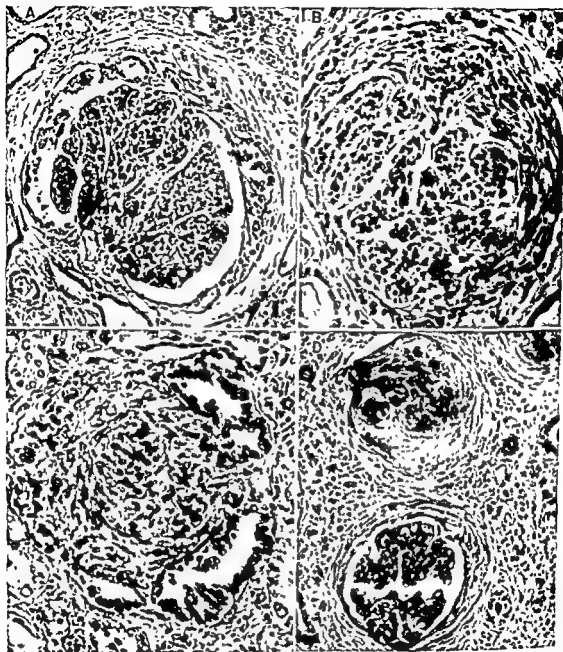


FIG A Crescent of subacute diffuse glomerulonephritis made up of proliferated epithelial cells. The remainder of the malpighian tuft shows the picture of proliferative and early lobular glomerulitis.

FIG C "Adenoid formation" in crescent of chronic glomerulonephritis.

FIG B Crescent in more advanced stage than that shown in figure A. The epithelial cells have elongated, become fibroblastic and the matrix has become collagenized.

FIG D Advanced stage of crescents of chronic glomerulonephritis with partial encroachment onto tufts.

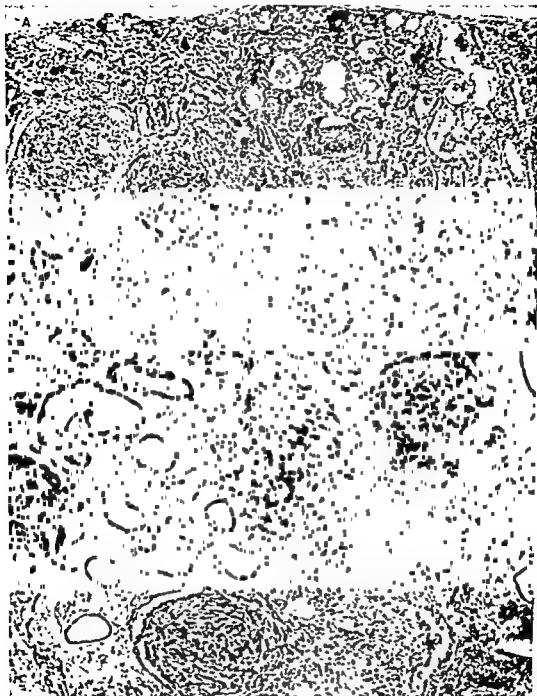


FIG. A *Subacute necrotizing glomerulonephritis*. The glomerular changes appear fulminant consisting of polymorphonuclear leukocytic inflammation, necrosis and disorganization of loops. The tubular atrophy and interstitial fibrosis, over and above the acute changes, show the process to be older than indicated by the glomeruli. However, the clinical history of the illness in this 29 year old male was only of three weeks' duration. (A. F. I. P. Ac. 111849)

FIG. B *Subacute glomerulonephritis of the exudative and proliferative type*. The glomerular and interstitial fibrosis indicate that the acute inflammation is an exacerbation or prolongation of a glomerulonephritis of subacute duration.

PLATE 63. SUBACUTE MEMBRANOUS GLOMERULONEPHRITIS ("LIPOID NEPHROSIS")

A

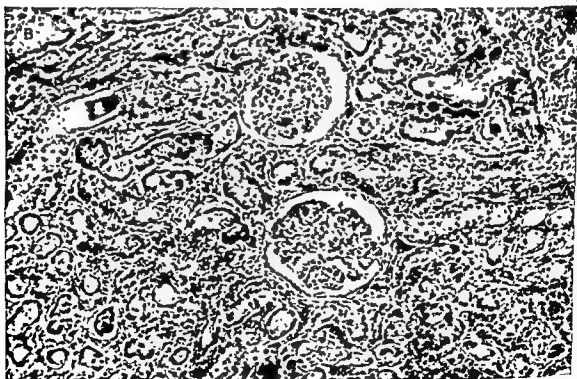
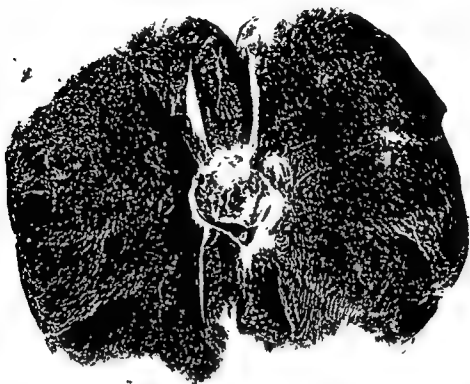


FIG. A "Large pale (white) kidney" of subacute diffuse glomerulonephritis. This swollen, nongranular kidney is the type associated with the clinical nephrotic syndrome.

toms of edema, nocturia or polyuria. At times, however, the presenting symptoms may be more covert and may consist of anorexia, headache, vertigo, dyspnea, impairment of vision, epistaxis, or gastrointestinal symptoms. Indeed, in some instances, uremia itself may actually initiate the clinical syndrome in the form of headache, vomiting and mental confusion. It might be well to consider some of the individual signs and symptoms separately.

### *Proteinuria*

Proteinuria is a long known and almost constant feature of chronic glomerulonephritis just as it is in the acute disease. When the albuminuria is abundant and protracted, it is followed by the clinical elements of the nephrotic syndrome: hypoproteinemia, reversal of the albumin-globulin ratio in the blood, hypercholesterolemia, and edema. In many cases, the degree of albuminuria decreases, therewith, the hypoproteinemia and edema clear. This occurrence is not a good omen, but, on the contrary, indicates a conversion of the large pale kidneys of lobular or membranous glomerulonephritis into the sclerotic, contracted kidneys. The progressive scarring of the glomeruli (rather than tubules) of these contracting kidneys reduces the leakage of protein.

### *Edema*

Edema of renal origin is closely linked with the loss of albumin and the resulting hypoproteinemia. Consequently, the edema is usually most marked in the early months or years of the disease and tends to disappear with the diminution in the degree of albuminuria. The albuminuria, as mentioned, lessens with progressive contraction of the kidney. In other words, the presence of appreciable edema in patients with contracted kidneys is generally of cardiac rather than renal origin. There is totally inadequate evidence for believing that edema in glomerulonephritis is caused by diffuse capillary damage throughout the body (i.e., so-called "nephritic edema"). There is no histologic evidence of such damage. Moreover, on the basis of more recent analyses there is no longer reason to believe, as was formerly thought, that fluid of "nephritic" edema (as

opposed to nephrotic or cardiac edema) contains a higher concentration of protein indicative of capillary damage. As previously indicated, Warren and Stead found the average concentration of protein to be 0.4 to 0.8 per cent in the edema fluid of patients with acute glomerulonephritis, this concentration is not significantly different from that in edema fluid of congestive heart failure.

### *Hypertension*

Hypertension has become so closely identified with glomerulonephritis that its absence in cases with the nephrotic syndrome has encouraged the point of view that such cases represent a basically different disease from glomerulonephritis. Actually, many patients with "lipoid nephrosis" do eventually develop hypertension, particularly as the glomerular changes—including glomerular ischemia or at least narrowing of the glomerular capillaries—progress. In children and young adults especially, it may be necessary to take daily readings of blood pressure to detect evanescent rises of both the systolic and diastolic pressures to the vicinity of 140/90. Especially in cachectic patients, hypertension may be absent or minimal, in some cases of associated myocardial insufficiency, a drop in a pre-existing high blood pressure may occur. Remissions of hypertension are likely to take place in the intervals between the exacerbations or recurrent attacks.

As a rule, the level of blood pressure in chronic glomerulonephritis is lower than that of essential hypertension and not as labile. However, striking exceptions occur. *Malignant hypertension* of severe degrees (e.g., 250/150) may be superimposed onto chronic glomerulonephritis just as it may complicate other renal diseases such as chronic pyelonephritis, or benign nephrosclerosis. Histologically, these cases of chronic glomerulonephritis show the typical vascular lesions of malignant nephrosclerosis in addition to the lesions of glomerulonephritis. The clinical differentiation of chronic glomerulonephritis from essential hypertension may be difficult or impossible to make, especially in the middle-aged patients. The hypertension in chronic glomerulonephritis may cause severe headaches from hypertensive encephala-



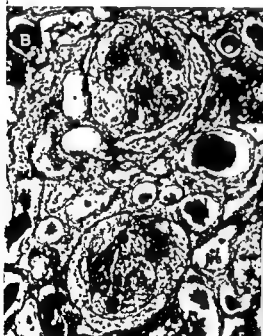
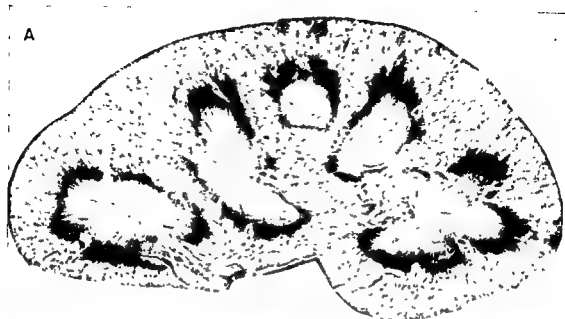
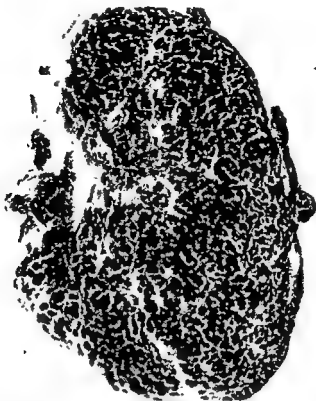


FIG. A Typically swollen pale kidney of subacute nephrotic glomerulonephritis

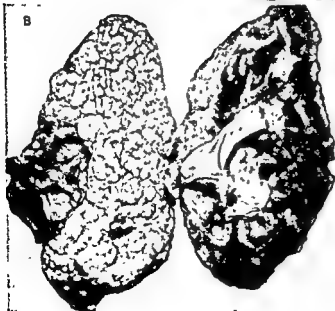
FIG. B Gnarled glomeruli from kidney illustrated in figure A. Patient had clinical nephrotic syndrome plus hypertension. Note the glomerular protein exudation and the tubular casts. This glomerular picture is distinctly unusual with the nephrotic syndrome (Mallory-Heidenhain stain).

FIG. C Doubly refractile maltese crosses of cholesterol esters in epithelium of proximal convoluted tubules from kidney illustrated in figures A and B.

A



B



C



FIGS A, B AND C *Chronic sclerosing glomerulonephritis*, the secondary contracted pale kidney with large, somewhat pale and irregular granulations (figures A, B, and C) in contrast with the redder, more irregular and finer granulations of benign nephrosclerosis and with the coarse scarring of the contracted kidneys of chronic pyelonephritis and that of multiple infarcts (plate 186A)

lopathy just as in essential hypertension, and on occasion may lead to death from cerebral hemorrhage or cardiac insufficiency. More commonly, the effect of the hypertension is cardiac hypertrophy, designed, so to speak, to compensate for the progressive destruction of the renal parenchyma. Eventually even the high level of the blood pressure is too low and the myocardium too weak to maintain adequate renal blood flow and clearance, as well as enough of a polyuria through the severely scarred kidneys, and death occurs from renal insufficiency.

### *Retinopathy*

Hypertensive or arteriosclerotic retinopathy is present in almost every case of chronic sclerosing glomerulonephritis (Cannady and O'Hare) and is as ominous a prognostic sign as it is in other types of hypertensive diseases. It usually portends death within one to two years. Failing of vision, rarely almost blindness and scotoma for certain colors, especially blue, occurs with the retinopathy. Retinal detachment which is often bilateral, is a particularly serious complication of hypertensive retinopathy in chronic glomerulonephritis as well as in malignant hypertension in general, although the detachment may correct itself if it occurs in association with toxemias of pregnancy. The retinopathy is correlated with the level of hypertension rather than the degree or type of renal impairment (plate 211 C-G).

*Exophthalmus* is observed occasionally in cases of chronic glomerulonephritis and is presumed to be related to the hypertensive encephalopathy.

### *Renal impairment*

One of the bewildering features of chronic glomerulonephritis is the variable tempo of renal deterioration not only from case to case but in individual cases. The range of time from the initial insult to the final decompensation may be from months in some instances to decades in others.

Latent extrarenal infections, anamnestic renal reactions, the possible additional load of certain elements in the diet, and the unaccountable progression of fibrosis in different

parts of the nephron are all factors which vary enormously in their influence on renal morphology and function. How to control such relentless influence is the great problem in nephritis.

### *Urine*

The proteinuria in chronic glomerulonephritis is almost constantly accompanied by a variety of casts including hyaline, granular, epithelial and fatty casts. There is a fairly close relationship between the albuminuria and the casts. As the albuminuria diminishes with contraction of the kidney, the numbers of casts become less until only an occasional hyaline cast is present. However, in the terminal stages, the large "renal failure" casts of Addison are commonly seen (plate 71). In those cases of abundant albuminuria associated with the nephrotic syndrome, birefringent lipids—either free or in epithelial cells—are found in the sediment (plate 73). These lipids are present in the urinary sediment of other cases with the nephrotic syndrome including amyloidosis, diabetic glomeruloclerosis and syphilitic nephrosis.

Hematuria of slight degree is usually present in cases of chronic glomerulonephritis in the contracted stage. Little or no hematuria is observed in patients with the large pale kidneys of chronic membranous or lobular glomerulonephritis. If abundant hematuria is present in chronic glomerulonephritis, an acute exacerbation or a complicating malignant nephrosclerosis should be suspected. The relatively greater hematuria is a pinch of evidence in favor of the diagnosis of chronic glomerulonephritis as against amyloidotic nephrosis or diabetic glomerulosclerosis.

### *Specific gravity*

Often renal impairment may be compensated for many years by the capacity of the body to produce excessive amounts of urine. The polyuria of the order of 2 to 3 liters tends to yield an isotonic urine of a specific gravity of 1.010 (isosthenuric), or slightly less (hyposthenuric) with very little range. At the same time, the inability to concentrate the urine is somewhat neutralized by the release of sufficiently large

A

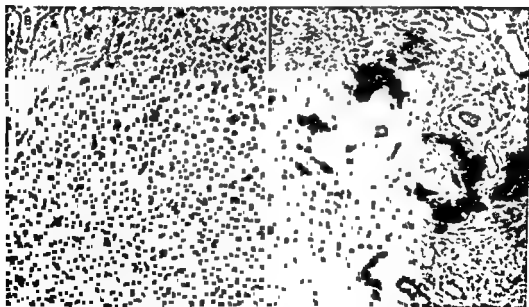
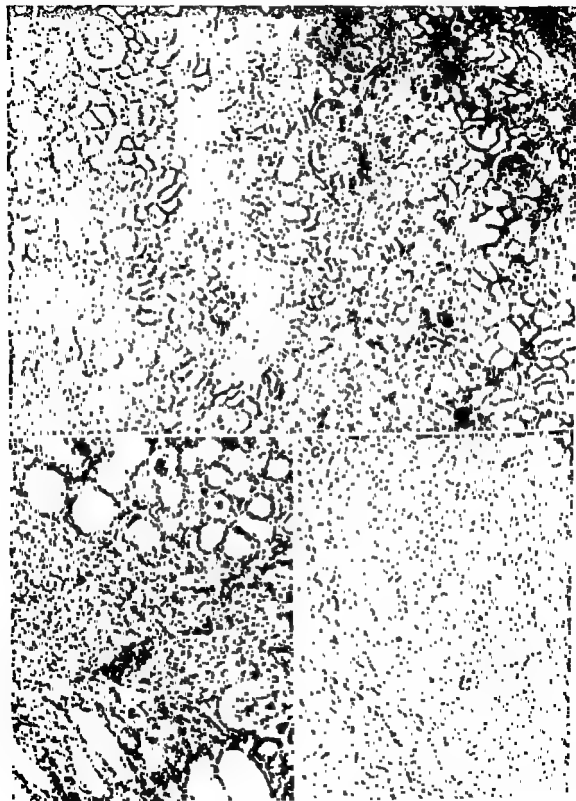


FIG A Chronic sclerosing glomerulonephritis in the contracted stage in contrast to the normal kidney below

FIG B Secondary parathyroid hyperplasia in chronic sclerosing glomerulonephritis with renal insufficiency

FIG C Chronic sclerosing glomerulonephritis with metastatic calcification in association with secondary parathyroid hyperplasia

PLATE 69. CHRONIC SCLEROSING GLOMERULONEPHRITIS



(Legends on facing page.)

quantities of glomerular filtrate. With polyuria there is associated nocturia and polydipsia although the patient may nevertheless appear dehydrated. In this compensated stage of renal impairment there is no azotemia, but when the polyuria is reduced, as from an accompanying myocardial failure, renal insufficiency with azotemia develops and uremia appears shortly. The reduction of urinary output in this last phase of the disease is not characterized by an elevation of the specific gravity as in the oliguria of normal kidneys. The tubules still do not possess an ability to concentrate the urine so that the specific gravity persists at about the level of 1.010. Such impairment of concentrating capacity is unusual in acute glomerulonephritis because destruction or dysfunction of the tubules only exceptionally is so marked in this early stage.

### Blood

Anemia, of the secondary or normochromic type, is generally given much weight in the differentiation of chronic glomerulonephritis from other diseases. The anemia may be profound and may reach counts of less than 2,000,000 red cells per cu. mm. Occasionally, a picture simulating pernicious anemia occurs in association with chronic glomerulonephritis, and Townsend and his associates have found evidence also of diminished gastric acidity. The relationship to pernicious anemia is undoubtedly coincidental. At the same time, the mechanism of the anemia still needs to be explained. There is a positive correlation between the degree of renal impairment and the anemia (Townsend). The marrow is normal or hyperplastic, not megaloblastic. The platelet count is not remarkable. The current thought on the mechanism is that probably several factors are concerned: (1) blood destruction, (2) blood loss in the urine, and (3) diminished blood forma-

tion as a result of some toxic influence on the marrow (Emerson).

### Osteodystrophy

The changes in bones and parathyroid glands are described in the sections on hyperparathyroidism and renal rickets.

## CHRONIC SCLEROSING GLOMERULONEPHRITIS

### Pathology Gross Appearance

As some of the inflamed glomeruli and their appertaining tubules become atrophic and fibrotic while others become hypertrophied, the soft smooth white kidney develops pits and fine yellowish-grey protruding nodules on its capsular surface (plates 67, 68 A). These changes constitute the grossly visible granules which are distributed rather uniformly over the capsular surface. The crest of the granule corresponds to the hypertrophied dilated tubules, and the intervening depressed troughs to the atrophic nephrons. The overlying capsule becomes thickened and may become adherent particularly to the depressed scarred areas so that when the capsule is removed some of the cortex may be torn away. Occasionally small cortical glomerular and tubular cysts are present.

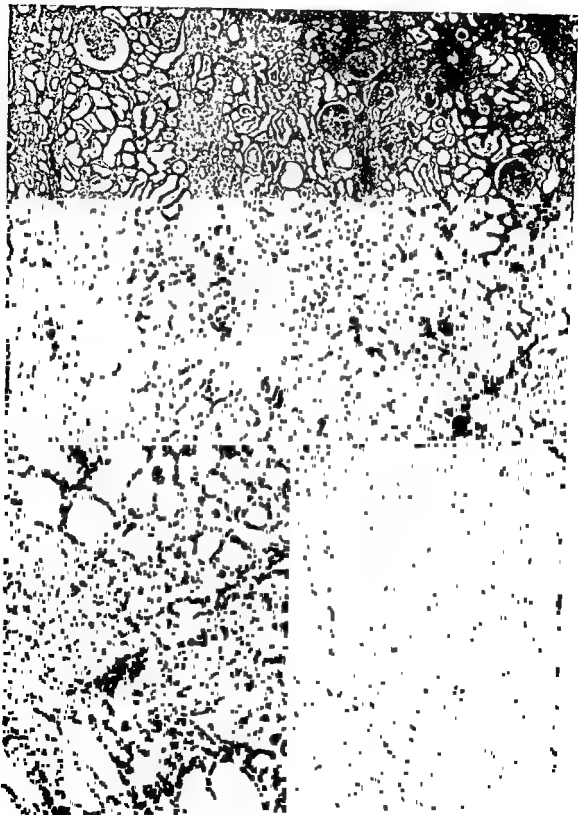
The contraction may be so extreme that the kidney may weigh from 30 to 50 Gm. and may have to be differentiated from a hypoplastic kidney. Occasionally, however, the nephritic kidney, even though scarred, may in fact weigh much more than the normal because of the extent of the compensatory hypertrophy of nephrons. The transformation from the "large white" to the secondary contracted "small pale" kidney may occur over a period of from two to five years, or many more, depending on such factors as the extent of initial renal involvement and the number and degree of the exacerbations.

FIG. A Low power view of section of chronic sclerosing glomerulonephritis showing the atrophic nephrons adjacent to the dilated tubules of hyperplastic nephrons.

FIG. B Interstitial fibrosis of chronic sclerosing glomerulonephritis showing marked argyrophilia of the interstitial fibers (Wilder stain).

FIG. C Thickened adherent capsule in chronic sclerosing glomerulonephritis showing contiguity between the argyrophilic fibers of the capsule and those of the atrophic renal parenchyma (Wilder stain).

PLATE 69. CHRONIC SCLEROSING GLOMERULONEPHRITIS



(Legends on facing page.)

quantities of glomerular filtrate. With polyuria there is associated nocturia and polydipsia although the patient may nevertheless appear dehydrated. In this compensated stage of renal impairment there is no azotemia, but when the polyuria is reduced, as from an accompanying myocardial failure, renal insufficiency with azotemia develops and uremia appears shortly. The reduction of urinary output in this last phase of the disease is not characterized by an elevation of the specific gravity as in the oliguria of normal kidneys. The tubules still do not possess an ability to concentrate the urine so that the specific gravity persists at about the level of 1.010. Such impairment of concentrating capacity is unusual in acute glomerulonephritis because destruction or dysfunction of the tubules, only exceptionally is so marked in this early stage.

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The contraction may be so extreme that the kidney may weigh from 30 to 50 Gm. and may have to be differentiated from a hypoplastic kidney. Occasionally, however, the nephritic kidney, even though scarred, may in fact weigh much more than the normal because of the extent of the compensatory hypertrophy of nephrons. The transformation from the "large white" to the secondary contracted "small pale" kidney may occur over a period of from two to five years, or many more, depending on such factors as the extent of initial renal involvement and the number and degree of the exacerbations.

FIG. A. Low power view of section of chronic sclerosing glomerulonephritis showing the atrophic nephrons adjacent to the dilated tubules of hyperplastic nephrons.

FIG. B. Interstitial fibrosis of chronic sclerosing glomerulonephritis showing marked argyrophilia of the interstitial fibers (Wilder stain).

FIG. C. Thickened adherent capsule in chronic sclerosing glomerulonephritis showing contiguity between the argyrophilic fibers of the capsule and those of the atrophic renal parenchyma (Wilder stain).





FIG. A *Chronic sclerosing glomerulonephritis with fairly uniform and diffuse fibrous obliteration of lumens of glomerular capillaries, interstitial fibrosis and tubular dilatation and atrophy.*

FIG. B *Chronic sclerosing glomerulonephritis showing various stages in the progression of the scarred glomeruli. The hyperplastic dilated nephrons, in general, belong to the large, relatively salvaged glomeruli. The "aglomerular nephrons" constitute a possible debatable exception.*



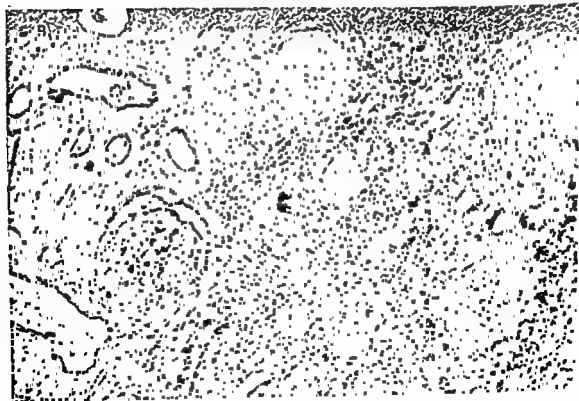
FIG A Chronic sclerosing glomerulonephritis with thin, apparently recent, protein hyaline casts in distal convoluted tubules

FIGS B AND C Dense hyaline casts of chronic sclerosing glomerulonephritis. Those of figure C especially simulate the protein casts of the myeloma kidney but lack the giant cells

FIG D Dense epithelial and granular renal failure casts in collecting tubules of chronic sclerosing glomerulonephritis

PLATE 72. CHRONIC SCLEROSING GLOMERULONEPHRITIS IN  
HYPOPLASTIC KIDNEYS

A



(Legends on facing page)

In cutting the kidney, the shrunken parenchyma offers considerable resistance to the knife. The cortex is distinctly narrowed and so irregular that in places the medulla may extend practically to the capsule. The normal markings are obscured and grey, fibrous streaks or yellowish fatty foci mottle the surface. The arteries may be appreciably thickened and, indeed, in this advanced stage, the gross picture may be indistinguishable from that of the primary contracted "vascular" kidney. As in most instances of renal atrophy, no matter the cause, the pelvic fat tends to be increased in proportion to the atrophy (plate 278 C).

The granularity of the surface of the kidney in chronic sclerosing glomerulonephritis tends to be a shade coarser, paler, and somewhat less uniform than the fine granularity of benign nephrosclerosis (plate 67, 209 A). The surface irregularity caused by chronic pyelonephritis, arteriosclerosis and multiple infarctions is considerably more marked (plates 186, 207, 260).

### *Pathology Histologic Appearance*

#### *Glomeruli*

Histologically few glomeruli are spared change. The interval between glomeruli is necessarily diminished in the contracted kidney of chronic glomerulonephritis, but these distances tend to be fairly equal. This situation also exists in benign nephrosclerosis but is in sharp contrast to the compact clusters of glomeruli in chronic pyelonephritis, or in infarcted areas. Although few glomeruli remain normal in chronic sclerosing glomerulonephritis, there is a wide range in the degree of involvement of individual glomeruli. Some may be reduced to a densely collagenized sphere in which the tuft has been tightly fused with the thickened Bowman's capsule and the whole glomerular unit reduced in size (plate 70 A), others show only partial eccentric fibrosis with varying degrees

of adhesion of capillary loops to each other and to Bowman's capsule (plates 70 B, 71 A). The portions of such tufts that have escaped the obliterative fibrosis present in adjacent loops tend to be ischemic and to show some thickening of the basement membranes. In general there is a parallel between the degree of fibrosis of the tuft and Bowman's capsule. Commonly in this type of glomerulonephritis the few glomeruli that are not injured are larger in diameter, sometimes about twice the normal size, as if stimulated to compensatory hyperplasia.

#### *Tubules*

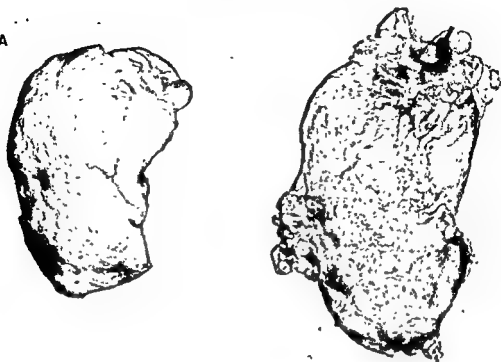
If we accept the classical notions that the tubules are dependent on the integrity of the glomeruli for the predominant source of their blood supply, then in diffuse glomerulonephritis we should expect profound tubular damage. The fact is that the tubular damage varies considerably and it is by no means possible always to correlate the degree of tubular alteration with the amount of glomerular change. Usually there is some tubular degeneration in association with glomerulonephritis which may take the form of fatty changes in the proximal convoluted tubules, epithelial desquamation, polymorphonuclear leukocytic infiltrations, casts and foci of frank necrosis. Occasionally there is marked necrosis of tubular epithelium in great disparity with the glomerular change, at other times, there may be striking glomerular damage with little apparent alteration of the tubules. It would seem therefore that other factors must play a role in the glomerulo-tubular relationship. The evidence leads one to suspect that the dependence of the tubules on the glomerulus and its efferent arteriole, although usually great, is far from necessarily complete. The amount of nourishment supplied to the tubules from the afferent arteriole



FIG. B Chronic sclerosing glomerulonephritis. Section taken from the kidneys illustrated above. The fibrosis of the glomeruli and interstitium and the arterial and arteriolar sclerosis in this child's kidneys are indistinguishable from the corresponding changes in adults.

PLATE 72 . CHRONIC SCLEROSING GLOMERULONEPHRITIS IN  
HYPOPLASTIC KIDNEYS

A



(Legends on facing page )

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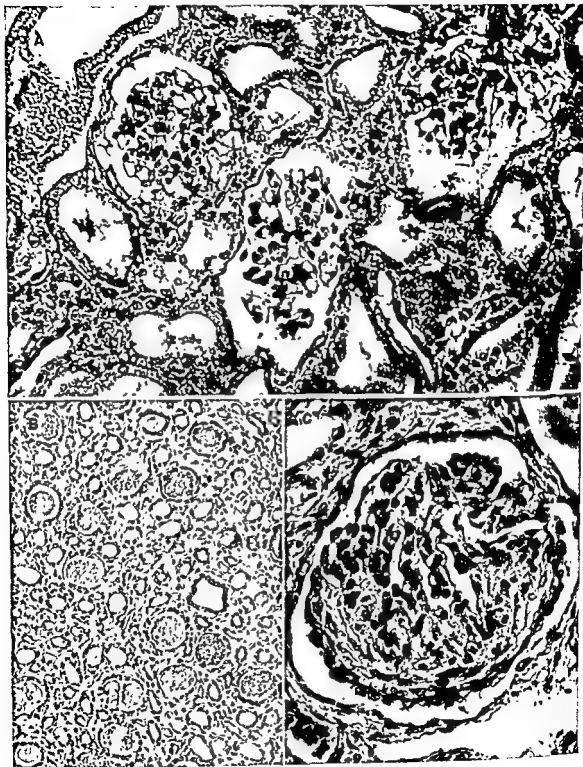
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FIG A Hypoplastic kidneys which also show evidence of chronic sclerosing glomerulonephritis. Anomalous kidneys are, in general, more vulnerable to inflammation than normal kidneys. The possibility cannot be excluded that these kidneys were of normal size at birth and that the glomerulonephritis and contraction occurred early in childhood.

FIG B Chronic sclerosing glomerulonephritis. Section taken from the kidneys illustrated above. The fibrosis of the glomeruli and interstitium and the arterial and arteriolar sclerosis in this child's kidneys are indistinguishable from the corresponding changes in adults.

PLATE 73. CHRONIC MEMBRANOUS GLOMERULONEPHRITIS  
("LIPOID NEPHROSIS")



(Legends on facing page )

via Ludwig's vessel and from shunts off the interlobular and arcuate arteries may, under abnormal conditions, be considerable

Many of the nephrons, however, do undergo atrophy following the lead of the glomerulus. Such atrophic nephrons take the form of small tubules isolated in a contracted focus of fibrous tissue which, grossly, constitutes the depressed areas between the granules (plate 69). The tubules of the intervening nephrons are inclined to undergo hyperplasia, hypertrophy and often dilatation, a process ascribed teleologically to compensation. These hypertrophied tubules usually, but not necessarily, associated with a relatively intact or hypertrophied glomerulus, make up the crest of the granules observed on the surface of the kidney

### Interstitium

As stated, in the acute phase of glomerulonephritis the interstitium may be edematous and focally infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells. In later stages, the edematous stroma is replaced by firm, generally well vascularized stroma which contains abundant reticulin fibers. The preponderance of the interstitial fibrosis was responsible for the former application of the term "chronic interstitial nephritis" in many instances of chronic glomerulonephritis, but it now seems clear that the interstitial scarring is quite secondary to the glomerulonephritis. Foci of cellular infiltration form a constant part of the picture, the cells consisting principally of lymphocytes, histiocytes and plasma cells. Occasionally deposits of doubly refractile lipids are found in the stroma just as they are in the tubular epithelium, especially in chronic membranous or lobular glomerulonephritis (plate 76)

### Vascular changes

As the glomerulonephritis progresses there is greater likelihood of the development of one or more varieties of vascular change. Although in the acute stage of glomerulonephritis there may be no evidence of extraglomerular vascular disease, it is important to emphasize that in the later stages the degree and type of vascular involvement may so closely simulate the changes in the primarily vascular kidney as to make differentiation impossible on the basis of examination of the vessels alone. The changes may take one of the following forms: (1) endarteritis obliterans, (2) arteriosclerosis or (3) arteriolar necrosis

1 *Endarteritis obliterans* is represented simply by a sclerotic intimal thickening of arteries. It is the same process that results in the physiologic obliteration of the ductus arteriosus, for example. In chronic glomerulonephritis arteries of all sizes may be involved just as in the nonhypertensive "senile kidney." The elastic laminae are usually not reduplicated as in hyperplastic sclerosis although fine elastic fibrils may be scattered through the outer part of the intima. The intima may show fatty and hyaline thickening. The pathogenesis of this intimal change is not clear but it appears not to be related to hypertension. Histologically this form of endarteritis is quite like that found in association with nonspecific chronic inflammation as, for example, at the base of a gastric ulcer. Fishberg prefers to regard the arterial change as a consequence of obstruction to the flow of blood due to the obliterated glomerular capillaries

2 *Arteriosclerosis* is practically a constant feature of chronic glomerulonephritis in which there has been hypertension of some years'

FIG A Chronic membranous glomerulonephritis (lipoid nephrosis) of an infant aged 3 years, showing glomeruli that might perhaps be called normal but which in fact show increased cellularity, a delicate thickening of basement membranes and protein precipitate in Bowman's spaces. Fat is present in the tubules. The illness was of four months duration and followed an episode of whooping cough (A.F.I.P. Acc 39321)

FIG B Protein casts in collecting tubules from kidney of "lipoid nephrosis" illustrated in figure A

FIG C Unequivocal, unresolved glomerulitis from same case as illustrated in figure A, furnishing clue to the over-all glomerulopathic nature of "lipoid nephrosis"



PLATE 74 CHRONIC MEMBRANOUS (NEPHROTIC) GLOMERULONEPHRITIS  
("LIPOID NEPHROSIS")

A

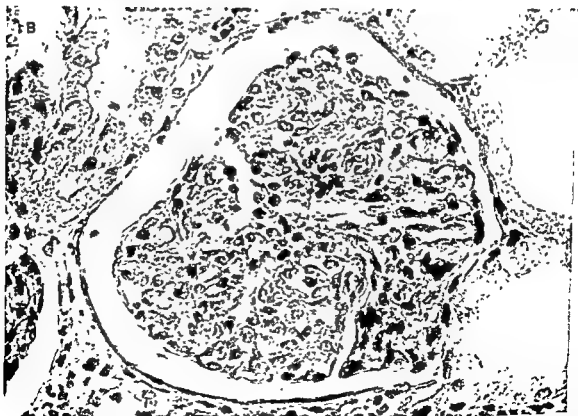


FIG A Chronic membranous glomerulonephritis showing the swollen (yellow) cortex associated with the clinical nephrotic syndrome in an adult

FIG B Membranous (and proliferative) glomerulonephritis from kidney illustrated in figure A. Patient had the clinical nephrotic syndrome in conjunction with hypertension. Note fat vacuoles in prox-



FIG A Abundant fat is present in the epithelium of the proximal convoluted tubules in this case of chronic membranous glomerulonephritis (Sudan III stain)

FIG B Doubly refractile fat in the epithelium of proximal convoluted tubules is observed with polarized light

FIG C Hyaline acidophilic granules are prominent in the epithelium of the proximal convoluted tubules. The assumption that the granules represent reabsorbed protein warrants re-examination, the granules more likely are the result of swollen intrinsic cytoplasmic constituents

ment membranes of the glomerular capillaries (plates 74 B, 78). Their walls are so rigid as to resemble bent wire even more closely than the glomerular "wire-loops" of disseminated lupus erythematosus (plate 79). However, the lesions of the latter are focal within any given tuft and are more brightly acidophilic than those of membranous glomerulonephritis. In addition, the increased thickness of the walls of the glomerular capillaries in membranous glomerulonephritis is rarely as great as it is in lupus erythematosus in which the walls often bulge in a verruciform fashion. Finally, the focal lupus lesion is often associated with an exudative glomerulitis in the remainder of the tuft, a feature not part of the picture of membranous glomerulonephritis.

Frequently in membranous glomerulonephritis, there are slight to moderate degenerative and regenerative changes of the tubular epithelium, particularly of the proximal convoluted tubules. Mild focal atrophy of the tubules with replacement fibrosis is common. Lipid, partially birefringent, is often present in the epithelium of the proximal tubules. Protein casts are common and a few casts of hemoglobin may also be present in the distal nephron. Inflammatory cells are sparse, but scattered foci of lymphocytes in the interstitium may occur. Usually no significant extraglomerular vascular changes are observed, except in the presence of protracted hypertension.

The changes just described are found in the straightforward cases of chronic membranous glomerulonephritis. However, the strikingly uniform glomerular changes may be altered by inflammation and distortion of the glomerular capillaries. Frequently, residual evidence of an antecedent membranous glomerulonephritis can be detected among the only partially scarred glomeruli of contracted kidneys. This is what usually happens in those patients whose clinical picture of the nephrotic syndrome is transformed into that of chronic sclerosing glomerulonephritis. As the glomeruli become progressively scarred, the large smooth, pale kidney shrinks and develops a granular surface. While this is happening, the albuminuria lessens, the edema tends to clear and renal insufficiency begins to appear.

*Chronic lobular glomerulonephritis.* In lobular glomerulonephritis, as in the membranous form, the lesion is diffuse, sparing no glomerulus (plate 80). The glomerular tufts are sharply lobulated into from four to eight hyalinized spheres of rather uniform size. There is some tendency for the periphery of each lobule to be laminated by two or three layers of endothelial cells although here and there a lobule is made up of a mass of cells (presumably mostly endothelial) with minimal stroma. Occasionally, the thickened capillaries running the spheres are dilated as in diabetic glomerulosclerosis, with which, incidentally, this lesion is commonly confused (plate 245).

The lobulation is sometimes referred to as lobular "simplification" of glomerular structure. This "simplification" is a superficial impression that is not supported by the facts of finer histologic study. For example, with routine hematoxylin-eosin stain, the lobules appear to represent merely hyaline thickening of "intercapillary" tissue. When stained with silver (for example, the modified Bielschowsky stain) it is of some surprise to note that the acidophilic spheres are, in reality, made up of small curlycoos of argyrophilic fibers, rather than a mass of intercapillary tissue. These fibers represent the walls of the glomerular capillaries distorted by irregular thickenings and proliferations, often in association with hyperplastic endothelial cells. There is no impressive reason to continue to believe that this material is simply a broadening of intercapillary tissue. The same problem arises in connection with the lesion of diabetic glomerulosclerosis, and is treated in more detail in the discussion of this lesion. It is clear that many who regarded the matter as settled a few years ago are now reconsidering the question of the role, or even existence of intercapillary tissue in these lesions. To reemphasize the point, in the case of lobular glomerulonephritis, as in diabetic glomerulosclerosis, as well as in amyloidosis of the glomeruli, the evidence indicates that the walls of the glomerular capillaries rather than the intercapillary tissue participate in the genesis of the lesions.

The tubular, interstitial and vascular changes



FIG A *Lipid filled histiocytes embolic to glomerulus in a case of death due to blast injury*

FIG B *Glomerular fat embolism following multiple bone fractures*

are similar to those of membranous glomerulonephritis

#### RELATIONSHIP OF MEMBRANOUS AND LOBULAR GLOMERULONEPHRITIS TO "LIPOID NEPHROSIS"

There are three principal varieties of widespread glomerular lesions characterized by hyaline lobulation of the malpighian tuft, these are amyloidosis, diabetic glomerulosclerosis and lobular glomerulonephritis (plate 245). It is of interest to note that each of these lesions, when widespread, is associated with the nephrotic syndrome. The pivotal feature of the nephrotic syndrome is the loss of protein, principally albumin, in the urine. The proteinuria is best attributed to the increased permeability of the glomerular capillaries. In the lobular tufts of these three lesions, the histologic evidence indicates that such increased permeability of the capillaries occurs as a result of their dilatation, their obviously altered basement membrane about the spheres, or the operation of both factors. In membranous glomerulonephritis, the basis for the proteinuria is the diffuse alteration of basement membranes which spares none of the glomerular capillaries.

Although the clinical features of "lipoid nephrosis" may be fully developed in diabetic glomerulosclerosis, and in renal amyloidosis, the specific features—both pathologic and clinical—of these two entities, permit their ultimate segregation from the category of "lipoid nephrosis." There remain, therefore, as the histologic counterpart of "lipoid nephrosis," two clearly definable forms of glomerulonephritis: (1) chronic membranous glomerulonephritis, and (2) chronic lobular glomerulonephritis. In the past, despite the efforts of Bell and others, the glomerulonephritic nature of "lipoid nephrosis" has been unbraced by emphasis on the possible presence of abnormal proteins with excessive permeability, on the overproduction of antidiuretic hormone, and on the presumed impairment of the capacity of the renal tubules to handle protein. However, none of these explanations has ever been shown to account adequately for the physiologic derangements of the symptom-

complex known as the nephrotic syndrome. The following summary of the glomerulonephritic concept of "lipoid nephrosis" seems in keeping with the bulk of evidence:

1 That "lipoid nephrosis" is the clinical set of signs and symptoms outlined above which occurs as a part of the picture of chronic glomerulonephritis; that it corresponds to the "degenerative stage" in Addison's terminology of glomerulonephritis; and that "pure" or "mixed" types of lipoid nephrosis represent degrees of glomerular alteration rather than intrinsically different diseases.

2. That "lipoid nephrosis" is in reality a definite variety of subacute or chronic (membranous or lobular) glomerulonephritis with specific histologic alterations of the glomeruli, which are less obvious in children than in adults. This diminished histologic glomerular reactivity may be said to be more or less characteristic of the glomeruli of children as opposed to those of adults.

3. That it is possible to interpolate, merely from a histologic examination of the sections of the kidneys, that the patients had had the nephrotic syndrome.

4 That the clinical syndrome centers about the loss of abundant protein in the urine with consequent hypoproteinemia and edema and reversal of the albumin-globulin ratio. The cause of the hypercholesterolemia is not clear, but the lipidemia is a concomitant of severe protracted albuminuria, whether the cause is glomerulonephritis, amyloidosis, or diabetic glomerulosclerosis.

5 That the much overemphasized difference between the "pure" (without hypertension, hematuria or renal insufficiency) and the "mixed" types is subordinate to the main issue, and is dependent on the relative degrees of ischemia and integrity of glomerular capillaries.

6 That, despite the frequent absence of overt antecedent infection in chronic membranous glomerulonephritis, or lobular glomerulonephritis, there is sufficient evidence of transitional histologic similarity to the sclerosing types of glomerulonephritis to lead us to believe that their etiology is related.

7 That the nephrotic syndrome charac-

PLATE 78 CHRONIC MEMBRANOUS GLOMERULONEPHRITIS ("LIPOID NEPHROSIS"):  
THE "LARGE WHITE KIDNEY"

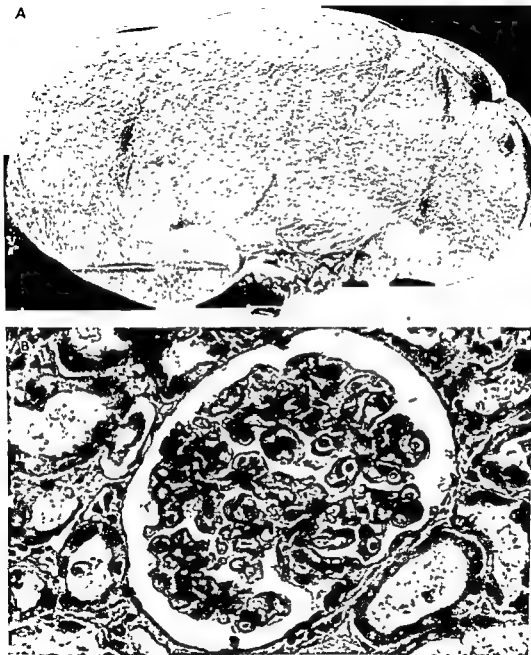


FIG. A The typical "large white kidney" of chronic membranous glomerulonephritis ("lipoid nephrosis")

FIG. B Glomerulus from the "large white kidney" of "lipoid nephrosis" illustrated in figure A. This glomerulus, quite representative of the remainder in this kidney, shows diffuse thickening of the capillary basement membrane, chiefly responsible for the term *membranous glomerulonephritis*. Such thick basement membranes are apparently astonishingly permeable to proteins.

teristic of chronic membranous or chronic lobular glomerulonephritis may persist to the end or may become altered to approach the clinical picture of chronic sclerosing glomerulonephritis, in accordance with the tempo in which the glomeruli are converted into those of the sclerosing variety (contracted kidney).

8. *That, because of the uniform, universally distributed collagenous alteration of the glomerular capillaries in chronic membranous glomerulonephritis, it would be of particular interest to learn the effect of ACTH especially on this individual form of the glomerulonephritides*

#### EXACERBATION OF CHRONIC GLOMERULONEPHRITIS

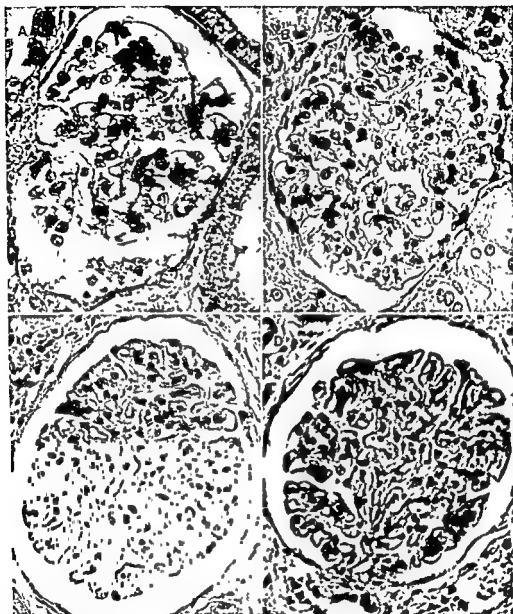
In many cases, exacerbations in chronic glomerulonephritis are known to be precipitated by overt infections. Nevertheless, in a large number of cases, the process of acute diffuse glomerulonephritis continues through the subacute and chronic states in the absence of apparent infections. The source of the momentum for the evolution of this series of changes is not altogether clear. If, for example, the child's initial acute glomerulonephritis followed an illness of scarlet fever, can it be supposed that the same glomerulitic agent smoulders for years afterwards, and produces, finally, the changes we recognize as subacute or chronic glomerulonephritis? Or, can we presume that there is sufficient propulsion supplied by the initial glomerulitic reaction to carry the disease slowly through its subsequent stages? Neither of these concepts seems entirely adequate to explain the clinical and histologic observations of most cases, except, perhaps, in some instances of membranous and lobular glomerulonephritis ("lipoid nephrosis").

The fact is that there is histologic evidence of exacerbation of glomerulonephritis in the form of acute glomerulitis superimposed onto various stages of chronic glomerulonephritis. It is likely that in many instances repeated nephropathic infections or reactions, such as respiratory infections or allergies, occur which are clinically undetected. On the other hand, one must reckon with the possibility that, after the first attack, a diminished number of glomeruli are left to carry on the original bur-

den of work. Under this condition, it is conceivable that the remaining glomeruli are more vulnerable to injury. Such injury may result, according to Addis, also from the excessive renal work imposed by a diet rich in proteins, a diet that would be innocuous to an individual with a normal number of glomeruli. By the same token, these handicapped kidneys may be particularly liable to other types of insults from infections that might spare normal kidneys.

With regard to many cases of chronic membranous or lobular glomerulonephritis ("lipoid nephrosis"), however, it appears probable that the initial damage may be self-perpetuating without histologically evident exacerbation. As already stated, the exaggerated permeability to proteins is the outstanding feature of the glomerular abnormality in these diseases; and it is plain, from a review of the bland, static-appearing, histologic picture of these entities—particularly of membranous glomerulonephritis—that essential maintenance of the histologic, and usually the physiologic, *status quo* responsible for the one sign (albuminuria) probably persists over most of the duration of the disease in many cases. As has been mentioned, however, at the time the clinical picture changes (that is, when the albuminuria and edema improve or even disappear) the process of glomerular sclerosis, tubular atrophy, and interstitial fibrosis begins, and the contraction of the large white kidney is initiated. At this time, too, hypertension and progression of renal tubular dysfunction tend to replace the nephrotic syndrome. When all this occurs, the common infectious, allergenic, or anamnestic factors, leading to exacerbation of glomerulonephritis in general, in all likelihood have superimposed their effects on these membranous or lobular forms.

Stated in other words, chronic membranous as well as chronic lobular glomerulonephritis may persist as such to the termination of the disease without histologic evidence of acute or progressive glomerular change. In such instances, the clinical picture is very likely to be that of the so-called "pure" lipoid nephrosis. In other cases, to repeat, the membranous or lobular glomerulonephritis may, with exacer-



FIGS. A to D represent increasing degrees of thickening of glomerular capillary basement membrane. Figure A is characteristic of the infantile type, these glomeruli rarely seem to be able to respond after the fashion observed in adults as in figure B. Figures C and D, often mistaken for the "wire-loops" of lupus erythematosus, are pathognomonic of the clinical nephrotic syndrome by virtue of the diffuseness of the changes in the basement membranes which involve all the glomeruli.



bations, evolve into the contracted kidney of chronic sclerosing glomerulonephritis. This is to say, again, that the type 2 of Ellis may become type 1, rarely does the reverse occur. Similar renewal of glomerular insults occurs in all of the other forms of glomerulonephritis. The exacerbation takes the form of acute, exudative, proliferative, or necrotizing inflammation, not only of the previously spared glomeruli, but of those glomeruli that have already been altered (plate 81). Among the latter, those portions of the glomerular tuft that have not become fibrotic may show the acute changes in the capillary loops (plates 81, 82). Moreover, we have observed that the collagen of even scarred segments of glomeruli may show evidence of exacerbation in the form of acute fibrinoid degeneration (plate 82). It is an interesting fact, observed by many investigators, and especially emphasized by Seegal and Earle, that the latent period between the original infection and the development of acute glomerulonephritis is longer than that which precedes the subsequent infections and exacerbations. The latent periods of the exacerbations may often be shortened to 24 hours, suggesting prior sensitization or anamnestic reaction. Again this feature contrasts with the usually equal intervals between infection and recrudescence of rheumatic fever, notwithstanding prior sensitization. The reasons for these diverse immuno-allergic responses are not known.

#### FOCAL GLOMERULONEPHRITIS

Four forms of focal glomerulonephritis occur:

- 1 Focal nonsuppurative glomerulonephritis
- 2 Focal suppurative glomerulonephritis
- 3 Focal endocarditic glomerulonephritis

#### 4 "Wire-loop" glomerulonephritis of disseminated lupus erythematosus

Although it may be entirely impossible always to distinguish some of these forms clinically, they are histologically and probably pathogenetically distinct.

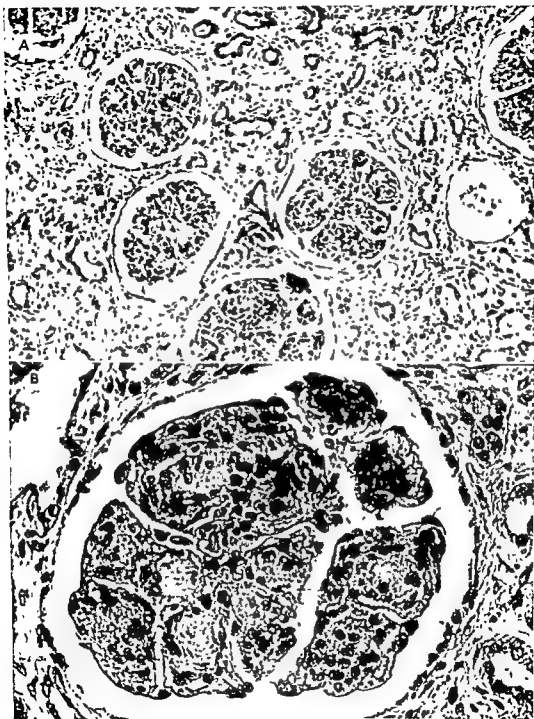
#### *Nonsuppurative Focal Glomerulonephritis*

Acute nonsuppurative glomerulonephritis ["infektnephritis" (Munk) or "herdnephritis"] may complicate any of a great variety of infections, chemical poisonings (for example, mercuric chloride and arsenic) and allergic reactions to a number of drugs, particularly the sulfonamides (plate 139). The infectious diseases may be bacterial, viral, rickettsial and may be due even to fungi (plate 57 D) or treponemas (for example, relapsing fever), the presence of bacterial endocarditis is not necessary for its occurrence. The clinical evidence of focal nephritis is generally minimal and consists of hematuria, albuminuria, and casts and leukocytes in the urinary sediment. For all clinical purposes, the lesions clear promptly if the primary disease is survived. Unlike many of the lesions of acute diffuse glomerulonephritis, the focal lesions occur at the height of the primary infection, rather than during the convalescence. This fact and the questionable assumption that bacteria are present locally have led to the conclusion (Fishberg) that focal lesions are due to the direct action of invading bacteria and other agents in contrast to the allergic nature of diffuse glomerulonephritis. This thesis is difficult to support on histologic grounds.

The vast majority of lesions of acute focal nonsuppurative glomerulonephritis have the individual glomerular pattern of any of the forms of acute diffuse glomerulonephritis. In

FIG A Chronic lobular glomerulonephritis of the type characterized by lobules of hyalinized glomerular capillaries. The clinical picture is typically that of the nephrotic syndrome. The lobules are much more diffuse and uniform in size than those of diabetic glomerulosclerosis. This lobular picture may be combined with sclerosing glomerulitis, in which case the clinical picture is correspondingly altered.

FIG B Chronic lobular glomerulonephritis from figure A. The hyalinized lobules superficially simulating diabetic glomerulosclerosis consist of masses of capillaries generally with a dilated loop at the periphery of the lobule. The silver stain reveals the entangled capillary masses in the lobules in contrast to the orderly lamination of silver fibers of diabetic glomerulosclerosis (compare plate 243).



(Legends on facing page)

other words, the focal glomerular change may be proliferative, exudative, necrotizing, hemorrhagic or a combination of any of these (plates 83, 84). No bacteria are found in the lesion, contrary to the usual description of them. Nor are they necessarily or even commonly associated with excretion abscesses unless they are of the suppurative type (plate 84 B). In other words, these forms of acute focal glomerulitis are also regarded as a toxic or allergic response to the products of organisms or drugs. To deny, as some do, that focal allergic reactions occur in the kidney is to fail to give interpretive consideration not only to these lesions, but to others, such as those of lupus erythematosus focal endocarditic glomerulonephritis, acute focal vascular alterations and, of course, acute focal interstitial nephritis.

The nondestructive nature of most of the lesions of acute focal nonsuppurative glomerulonephritis allows for complete architectural resolution. However, some glomeruli are so extensively altered that they are destined to be scarred. It is therefore reasonable to assume that occasional scarred glomeruli in otherwise normal kidneys may represent the end result of acute focal glomerulonephritis appearing during a previous, perhaps forgotten disease. These obliterated glomeruli are manifestly of no clinical significance, but they may complicate the differential histologic diagnosis. It is possible that some examples of the so-called "congenital glomerulosclerosis" represent the endstage of a similar process, in other instances, ischemic atrophy appears to account for these focal lesions of infancy.

#### *Suppurative Focal Glomerulonephritis*

Relatively infrequently, there are found lesions of acute focal suppurative glomerulonephritis that are obviously produced by the direct action of the organisms themselves which have reached the glomeruli through the blood stream in sepsis or as bacterial emboli (plate 84 B). In such glomeruli, as a rule, only a portion of the malpighian tuft is altered, quite as would be expected with focal inflammation due to pyogenic organisms. The inflammatory response consists primarily of a clump of polymorphonuclear leukocytes with

a degree of destructive change in the glomerular capillaries that happen to be included in the focus. Not only may bacteria be found in this type of focal glomerulitis, but there may be associated excretion abscesses in the corticomedullary junction. However, it is to be stressed that this picture is the *unusual* one of acute focal glomerulonephritis.

#### *Focal Endocarditic Glomerulonephritis*

For reasons to be explained the term *focal endocarditic glomerulonephritis* is to be used here instead of *focal embolic glomerulonephritis* or multiple glomerular embolization. This lesion occurs in from 33 per cent (Bell) to 92 per cent (Bachr) of the kidneys in cases of subacute bacterial endocarditis (that is, endocarditis of more than six weeks duration). The incidence of the lesions in our own experience corresponds closely with that of Bell's as far as subacute bacterial endocarditis is concerned, but differs from his in that he has observed the lesion in 2.9 per cent of rheumatic endocarditis, in 7.1 per cent of acute primary bacterial endocarditis (less than six weeks duration) and in 5.8 per cent of secondary (focus of infection demonstrable) endocarditis. We have seen only four cases of this lesion in which no endocarditis was present but which were associated instead with allergic arteritis. Therefore we regard the lesion as strongly presumptive evidence of subacute bacterial endocarditis. It is possible that in some instances the so-called acute bacterial endocarditis existed longer than the six weeks of evident symptoms. It is also known that the lesion of bacterial endocarditis has been assumed to be absent when it is actually present but of practically microscopic dimensions. On the other hand, in view of the concept to be mentioned of the nonembolic nature of the lesions, it becomes reasonable that, in isolated instances, the glomerulitic lesion may occur without endocarditis but with some corresponding immuno-allergic state. It is of interest that in the so-called "bacteria-free stage" of subacute bacterial endocarditis, the glomerular complication is much more likely to be an acute diffuse glomerulonephritis than a focal endocarditic glomerulonephritis, occasionally the two forms coexist.

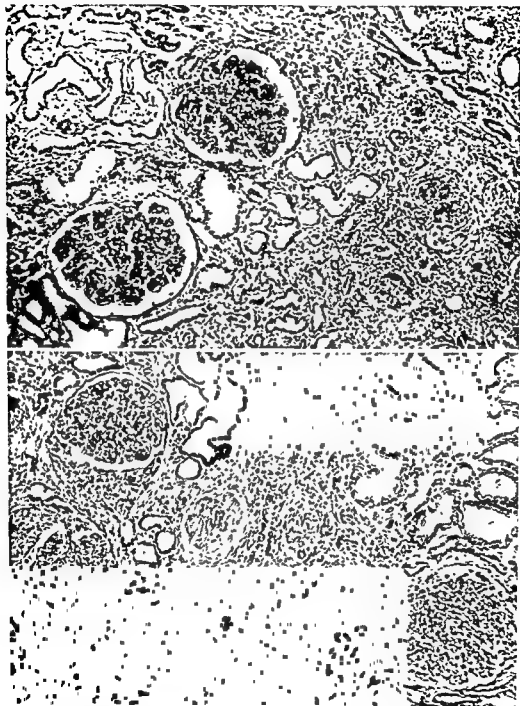


FIG A Chronic sclerosing glomerulonephritis with acute exacerbation as shown by the exudative glomerulitis in two large glomeruli on the left

FIG B Chronic sclerosing glomerulonephritis with acute exacerbation. In two glomeruli, the acute inflammation is present in the residual unobliterated portion of the malpighian tuft

### *Clinical picture*

As a rule, the lesions of focal endocarditic glomerulonephritis are so sparse or involve so small a portion of the malpighian tuft as to cause no apparent renal dysfunction. As new lesions occur, mild to moderate, sporadic, recurrent or persistent hematuria is usually the only indication of their presence. The hematuria must be differentiated from renal infarction. In occasional cases, the glomerular lesions may be so extensive as to interfere with renal function and may even lead to uremia. Of 23 cases of subacute bacterial endocarditis reported recently by Littman and Schaaf, 3 cases died with "renal failure" stated to have been produced by the focal glomerular lesions; in one of these patients, uremia was present. It remains to be determined whether or not antibiotic therapy of bacterial endocarditis will change the incidence of the various renal lesions associated with this disease.

### *Pathology*

*Gross appearance.* Grossly, the kidneys may appear quite normal. If the lesions are extensive, the kidney may be indistinguishable from that of acute diffuse glomerulonephritis, that is to say, it may be swollen, the cortex may be thickened and edematous, and the surface may be mottled with petechiae (plate 85 A).

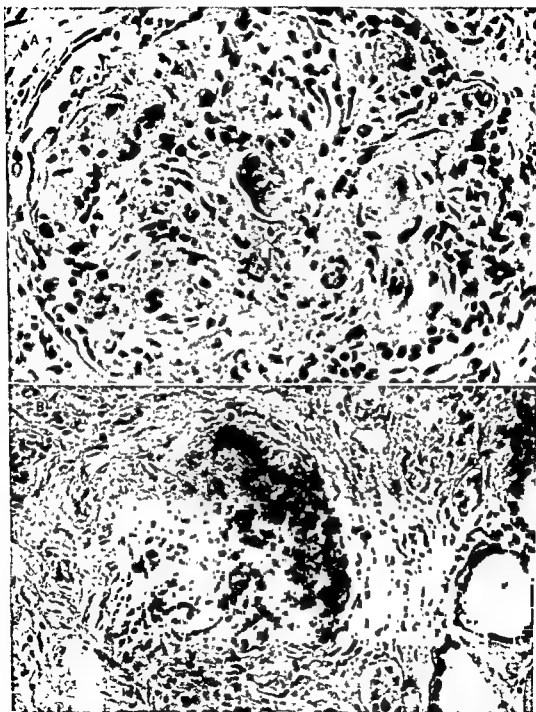
*Histologic appearance.* The lesion of focal endocarditic glomerulonephritis naturally varies with its duration. The earliest phase is characterized by a more or less circular focus of fibrinoid degeneration of collagen limited usually to one or occasionally two segments of the malpighian tuft and rarely involving the entire tuft. The hyaline mass consists actually of a fibrinoid coalescence of a few glomerular capillaries with their appertaining endothelial and epithelial cells. Often there is adherence of the lesion to Bowman's capsule. The endothelial or epithelial cells immediately adjacent to these foci may be swollen and basophilic very much as a regenerating tubular epithelial cell. Detailed study of the periphery of the lesion, especially at its junction with the adjoining portion of the tuft, discloses transition stages of capillary walls intermediate in degree

between the fibrinoid mesh of capillaries constituting the lesion and the unaltered ones of the remainder of the tuft (plates 85 B, 86). Silver stains, here too, reveal the argyrophilic fibers of the distorted glomerular capillaries (plate 86). Bacteria are very rarely found in these lesions.

The acute lesion, brightly eosinophilic and with a paucity of cells, becomes organized to form a densely hyalinized, hard collagenous segmental mass maintaining the essential configuration of the original lesion (plate 85 B). There appears to be no credible evidence to support the impression that the pathogenesis of the acute lesion is different from that of the healed one, contrary to other reports (e.g. Bell). Incidentally, in interpreting the argyrophilic fibers it must be remembered that fibrils in tissue undergoing collagenization may, in the presence of fibroblasts, show an argyrophilia that could be confused with the argyrophilia of degenerated collagen. This same problem obtains in the evaluation of changes in cardiac valvular verrucae (Allen). However, hematoxylin-eosin stained sections permit easy differentiation of a relatively acellular necrotic focus of fibrinoid material from a focus showing organization by healthy fibroblasts.

The lesion of focal endocarditic glomerulonephritis may spare the tuft altogether and involve merely the afferent arteriole in isolated instances. The quality of the fibrinoid alteration of the afferent arteriole in such instances is identical with that of the tuft itself. It is remarkable how little alteration occurs in those glomeruli in which the lumen of the corresponding afferent arteriole is severely compromised by the swollen necrotic arteriolar wall. Thrombosis is rarely seen in these lesions either of the arteriole or of the glomerular capillaries, although it is said to be characteristic of the acute lesion (Bell). Occasionally small crescents arise between the lesion and Bowman's capsule.

The portions of the tuft not specifically involved by the lesion are often altogether unaltered but in some instances take on the appearance of exudative or proliferative glomerulitis. Again, as in lupus erythematosus the number of glomeruli involved by this peculiar



FIGS. A AND B. Glomeruli from cases of chronic sclerosing glomerulonephritis with acute exacerbation. The exacerbation is represented by a focal fibrinoid degeneration (arrow) of the collagen of previously scarred glomeruli, indicating that such fibrous areas are not unreactive.

lesion may be few or many and the signs and symptoms obviously vary accordingly. In about 8 per cent of cases a sufficient number of glomeruli are involved extensively enough to cause renal failure. However, the glomerular damage is enough to cause frequent hematuria, and red blood cells may be found frequently in both the proximal and distal tubules in this condition. The formation of masses of hemoglobin in the distal nephron from laked red blood cells (plate 86 B) must not be confused with hemoglobinuric nephrosis. If the lesion is of some duration and severity, it may be associated with the type of tubular atrophy, interstitial fibrosis and focal interstitial inflammation that is seen in subacute or chronic glomerulonephritis.

#### *Reasons for nonembolic nature of focal endocarditic glomerulonephritis*

It is generally taught that the lesions of focal endocarditic glomerulonephritis are produced through embolization of particles of vegetations of subacute bacterial endocarditis. And, to be sure, the lesion is practically pathognomonic of subacute bacterial endocarditis, although a few cases have been recorded in its absence. Nevertheless, there are several convincing reasons for doubting the embolic pathogenesis of this lesion.

In the first place, bacteria are found with extreme rarity in these glomerular lesions. Second, the vegetations of acute bacterial endocarditis are often as large and as friable and about as prone to embolize as those of the subacute variety. Nevertheless, in cases of acute bacterial endocarditis (that is, bacterial endocarditis of less than six weeks duration) the lesions of focal endocarditic glomerulonephritis practically do not occur. The same situation obtains in Libman's "bacteria-free stage of subacute bacterial endocarditis." Third, focal endocarditic glomerulonephritis, as stated, has been reported, although rarely, to be sure, in the absence of subacute bacterial

endocarditis or other sources of emboli. Fourth, it would seem most unlikely for a vegetation to throw off hundreds of small emboli of about equal size into the general circulation, and for them to land in one organ to the practical exclusion of others. Finally, in instances of true septic emboli, clusters of bacteria often land in a glomerular capillary but fail to produce this lesion. Similarly, the inoculation of solid particles, as of potato agar, into the blood stream of an animal does not provoke this type of lesion.

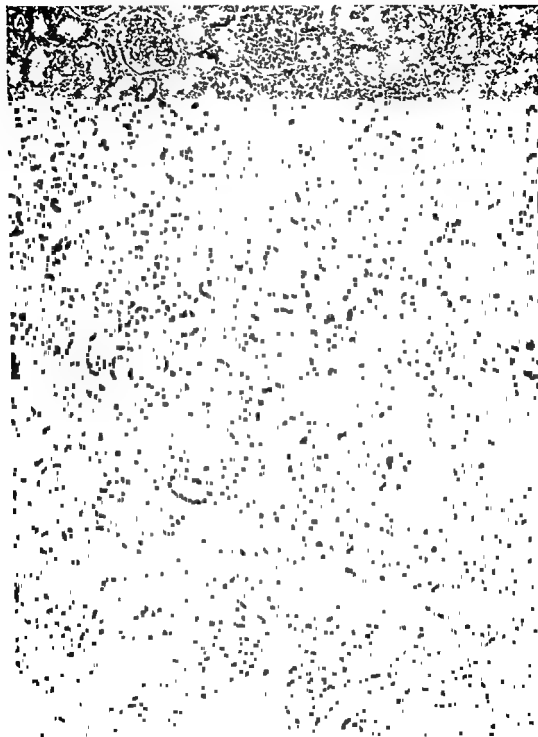
#### *Nature of focal endocarditic glomerulonephritis*

It is therefore our impression that the lesion of focal endocarditic glomerulonephritis represents an intrinsic fibrinoid reaction principally of glomerular capillaries but also of afferent arterioles. This reaction is not produced by the direct local action of bacteria but is very likely an immuno-allergic response presumably to the antigenic products of the bacteria and occasionally other allergenic agents, as in periarthritis nodosa. Such a concept explains more reasonably the absence of these glomerular lesions in acute bacterial endocarditis of a duration of six weeks or less, inasmuch as apparently greater time is required to set the stage for such an immuno-allergic response in this disease.

The occurrence of dense collars of plasma cells about some of the involved glomeruli is consistent with and suggestive of an immuno-allergic reaction rather than a reaction to the direct local infiltration of bacteria. This same principle applies to other infectious diseases, including the rickettsial diseases. No such capillary lesion similar to focal endocarditic glomerulonephritis is found in other organs, but then, neither is the "wire-loop" lesion of disseminated lupus erythematosus, the capillary diabetic glomerulosclerosis or the capillary lesions of glomerulonephritis found in other organs. The selective localization of these lesions to glomerular capillaries has been at-

FIG A Acute focal exudative glomerulonephritis (*Staphylococcus aureus* septicemia). The single affected glomerulus is in sharp contrast to the other uninvolved glomeruli. No bacteria were demonstrable in the section.

FIG B Acute focal necrotizing glomerulonephritis due to *Staphylococcus aureus* sepsis. No bacteria were demonstrable in the section.



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tributed to the relatively greater amount of blood that bathes glomerular in contrast to other capillaries, but this is probably not the complete answer

### DISSEMINATED LUPUS ERYTHEMATOSUS

Disseminated lupus erythematosus is characterized clinically by its rarity in males, prolonged fever, arthralgia, dysphagia, cutaneous telangiectatic rash especially of the cheeks and nose and the manubrial area of the chest, erythematous patches in the mouth, cardiac murmurs, pleuritic and peritoneal pain, leukopenia and thrombopenia. Remissions and exacerbations are common. The blood Wassermann test may give inconsistent results and may become falsely positive or anticomplementary, during the exacerbations. The gamma globulins of the blood are usually increased (Walker and Benditt). The "LE" cells are commonly present in the marrow and occasionally even in the peripheral blood (plate 96 C, D).

The disease runs its fatal course over a period varying from weeks, months, or years. Permanent recovery is said to occur (Baehr and Pollack) but such instances must be exceedingly rare. The remarkable selectivity of the female in this disease presupposes some hormonal linkage even though many of the histologic reactions are similar to those of allergy. Naturally, there comes to mind the fibrinoid reaction of vessels in animals treated with desoxycorticosterone (DCA) and related compounds in various situations of stress. A few instances of disseminated lupus erythematosus have occurred in males; these patients had no overt endocrinologic abnormalities.

In any individual patient only a few of the signs and symptoms listed above may occur, even the rash may be completely absent throughout the course of the disease. The clinical differential diagnosis of disseminated lupus erythematosus depends on the particular combination of signs and symptoms that are present. The list of such differential diagnoses includes rheumatic fever, subacute bacterial endocarditis, periarteritis nodosa, diffuse glomerulonephritis, scleroderma, dermatomyositis, trichinosis, and obscure infectious diseases, ob-

structing lesions of the esophagus and even surgical diseases of the abdomen because of the pain from the serositis.

### *Renal Lesions in Disseminated Lupus Erythematosus*

The kidneys of disseminated lupus erythematosus are generally somewhat larger than normal. Their surfaces are usually smooth but occasionally they are irregularly scarred and diffusely mottled with greyish and hemorrhagic areas or with petechial hemorrhages so as to resemble malignant nephrosclerosis or a form of acute diffuse glomerulonephritis (plate 88).

Histologically the tubules show very little change although in some instances hydropic vacuolization and marked hyaline droplet degeneration of the proximal tubules, often associated with slight fatty change, are prominent. Renal arteritis, simulating periarteritis nodosa, or any other arteritis is uncommon, contrary to the implication of the generally accepted cliché that the condition represents a diffuse vascular disease. Focal interstitial infiltration with lymphocytes, plasma cells and histiocytes is frequently present. Focal fibrinoid degeneration of stromal collagen is rarely found in the kidney in contrast to the incidence in the myocardium.

### *"Wire-loop" glomerulitis of disseminated lupus erythematosus*

In about 60 per cent of the cases of disseminated lupus erythematosus there is found a lesion of the glomeruli that is essentially pathognomonic of this disease, but with exceptions as will be indicated (plates 89, 90).

The glomerulitic lesions of lupus erythematosus is characterized by a focal, bright, acidophilic, homogeneous, generally nongranular thickening of one or more segments of the glomerular capillaries. Even in the flat plane of a section, the affected segments appear rounded by the usual presence of a fine high-light in the loop of the "wire." Bowman's capsule may show a similar focal fibrinoid degeneration. Unlike the less strikingly eosinophilic, evenly diffuse change in membranous glomerulonephritis (plate 91 A), the capillary wall of the lupus lesions may abruptly thicken

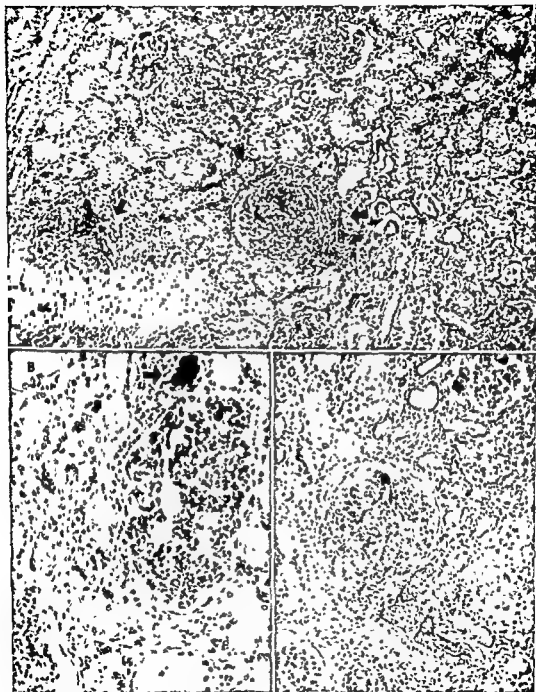


FIG A Acute focal proliferative and necrotizing glomerulonephritis (arrows) attributed to sulfathiazole therapy. Note the normal glomeruli in striking contrast to the altered glomeruli.

FIG B Acute focal exudative glomerulonephritis in *Staphylococcus sepsis* with bacterial embolus in afferent arteriole (arrow). This form of focal glomerulonephritis, unlike focal endocarditic glomerulonephritis, appears to be due directly to bacteria.

FIG C Acute focal glomerulonephritis with accompanying tubular necrosis following therapy of subacute bacterial endocarditis with bacitracin.

into an intralumenar mound, often mistaken for a fibrinous thrombus. This mound is really a form of verrucal capillaritis after the fashion of verrucal endocarditis or verrucal endocardiosis (Allen and Sirota), or the verrucal arteriolitis of typhus fever (Allen and Spitz). The fibrinoid material composing the wire-loop may take the stain for fibrin on the one hand or may stain as collagen does in its various intermediate stages of degeneration. In other words, with a Mallory-Heidenhain stain, the lupus lesion, even in a single segment, may vary from red to orange to blue, depending on the degree of degeneration of the capillary wall. Its affinity for silver is also variable but often appreciable (plate 244 D). This, too, is in harmony with the behavior of altered collagen or reticulin.

The wire-loop lesion may be associated with an otherwise normal tuft, or a tuft may be the seat of exudative or necrotizing glomerulitis, so severe as to show karyorrhectic disintegration of nuclei (plate 89 A). Capillary lesions corresponding to the wire-loop changes are not found in organs other than the kidneys.

As with other forms of focal involvement of glomeruli, for example, focal endocarditic glomerulonephritis or diabetic glomerulosclerosis, the degree of interference with renal function is obviously dependent on the number and extent of glomeruli involved. In other words, it can not be said categorically that the renal lesions in disseminated lupus erythematosus always lead to renal insufficiency. In some instances, the renal lesions are found only in isolated glomeruli. If most glomeruli are involved, renal insufficiency develops, as it does in about 39 per cent of cases. Some of these cases of disseminated lupus erythematosus with pretty nearly generalized glomerular involvement have in the past been classified merely as nonspecific acute or chronic diffuse glomerulonephritis.

Rarely, disseminated lupus erythematosus may be complicated by nonspecific diffuse glomerulonephritis. Rarely, too, lesions indistinguishable from the "wire-loop" changes are noted in eclampsia, scleroderma, glomerulonephritis, and malignant nephrosclerosis (plate 98).

In connection with the clinical diagnosis of the involvement of the kidney by lupus erythematosus, it is worth noting Krupp's observation that the Addis count in these cases revealed excessive red blood cells, red blood cell casts, fat oval bodies, epithelial and fatty casts, and large renal failure casts. In other words, the sediment is said to represent a telescoping of the findings of the three stages of glomerulonephritis.

#### *Extra-renal Lesions in Disseminated Lupus Erythematosus*

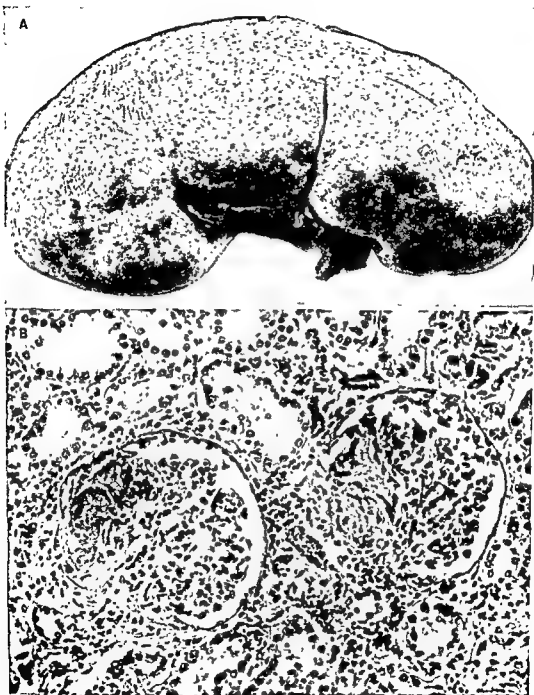
Because of the confusion regarding the terminology, the pathogenetic and morphologic concepts of disseminated lupus erythematosus, as well as the details of the histologic quality of the lesions of the kidney as opposed or as related to lesions in other organs, a summary of these lesions might be of some use. It is desired especially to try to define in this manner the various changes that occur in collagen and are important for the understanding of glomerular pathology.

One fact is immediately clear: although collagen and, in certain ways, reticulin have a limited range of histologically visible reactions to stimuli, there is nevertheless a sufficient number of categories of histologic change in this tissue that can be sharply defined and segregated. It is not at all trite to emphasize that just as not all hyaline looks alike, so not all fibrinoid degenerations of collagen look alike. And however nice these distinctions between the various forms of collagenous alteration

FIG. A Focal endocarditic glomerulonephritis showing characteristic petechial hemorrhages. This kidney would require differentiation grossly particularly from acute diffuse glomerulonephritis (plate 54) as well as from malignant nephrosclerosis (plate 211A).

FIG. B Focal endocarditic glomerulonephritis, from a case of subacute bacterial endocarditis. The

PLATE 85. FOCAL ENDOCARDITIC GLOMERULONEPHRITIS (FOCAL  
"EMBOLIC" GLOMERULONEPHRITIS)



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may be, they are not so veiled as to have their categorical nature concealed by adequately prepared routine sections stained with hematoxylin-eosin. This is not to say that special staining and fixing methods should not be used for definitive investigative studies (After all, the use of various silver, trichrome, lipid, glycogen and enzymatic stains, tryptic digestion and different fixatives such as xanthidrol, Zenker's and Regaud's solution, for the preparation of sections photographed and studied for this book demonstrates their specific usefulness.) This is to say, however, that for practical diagnostic purposes, routine sections serve in the instance even of the challengingly delicate and much mimicked changes of the collagenous diseases. What is required is an accurate visual evaluation of the granularity, acidophilia, homogeneity, location, shape, and form of the fibers, as well as of the accompanying inflammatory changes, or the lack of them.

### Skin

Three types of cutaneous lesions occur in lupus erythematosus. These are (1) chronic or discoid, (2) acute and (3) combined acute and chronic.

The *chronic or discoid* form of lupus erythematosus most often occurs in the skin over the malar regions and bridge of the nose but may also be found in the skin of other parts of the body. It is a scaly, red, indurated lesion. The histologic features include (1) alternating acanthosis and atrophy of the epidermis, (2) liquefaction degeneration at the dermo-epidermal junction, (3) dense collections of mononuclear cells, mostly lymphocytes, usually in the mid-dermis, (4) superficial hyperemia, (5)

keratotic plugging of follicles and (6) spotty parakeratosis (scaling) (plate 93). *Changes in collagen and blood vessels are not part of this picture* although statements to the contrary are in the literature. Chronic or discoid lupus erythematosus is rarely associated with the disseminated lesion.

The *acute lesion* of lupus erythematosus occurs on the face and upper chest particularly but may also involve the hands and mucous surfaces. Histologically it is characterized by a marked exaggeration of the liquefaction degeneration seen in the chronic form. The corium in this region is edematous and acidophilic, especially immediately adjacent to the epidermis where it may form an acidophilic band. The inflammatory cells include polymorphonuclear leukocytes, the nuclei of which tend to be elongated and otherwise distorted and fragmented (plate 93 B). Infrequently there is patchy fibrinoid degeneration of the dermal collagen and of the wall of an occasional vessel. If the diagnosis of lupus erythematosus, acute or chronic, were to rest on the finding of vascular degeneration in the skin, most of the cases would remain undiagnosed.

The *acute and chronic form* of lupus erythematosus is characterized by the combined features of the two types just described. In general it is impossible to distinguish histologically between the self-limited acute changes produced in a lesion of discoid lupus erythematosus by exposure to ultraviolet light, and those acute changes that occur as part of the systemization of the disease. Prognostication in such cases is guided by the facts that dissemination of the disease occurs relatively rarely in males, and rarely also as a complication of the chronic disease. Furthermore, clinical evidence of involvement of organs

FIG. A Focal endocarditic glomerulonephritis illustrating the early phase of fibrinoid necrosis in which the capillaries have not yet coalesced.

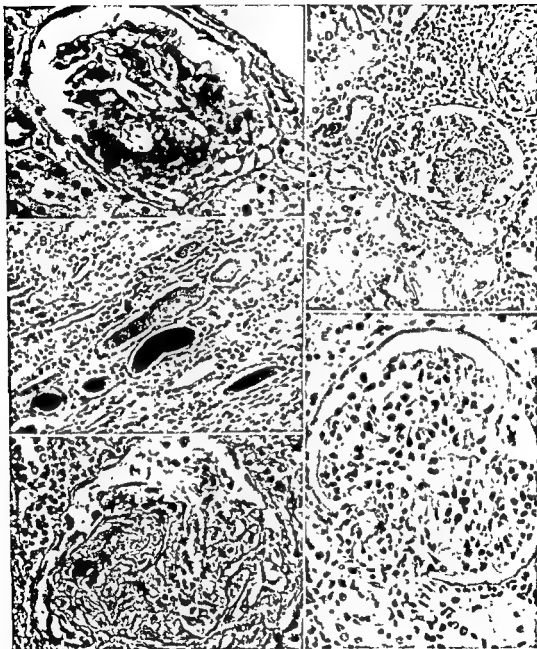
FIG. B Hemoglobin casts in focal endocarditic glomerulonephritis as a result of red blood cells having been fragmented in the tubules.

FIG. C Modified Bielschowsky's silver stain of focal endocarditic glomerulonephritis showing the congeries of silver fibers representing the residue of altered glomerular capillaries.

FIG. D Focal endocarditic glomerulonephritis showing the acute coalescent phase of fibrinoid degeneration of a portion of the malpighian tuft; the remainder of the tuft is essentially normal.

FIG. E True embolic glomerulonephritis in bacterial endocarditis showing embolus and polymorphonuclear leukocytic reaction. This lesion is obviously different from focal endocarditic glomerulonephritis.

PLATE 86 ' FOCAL ENDOCARDITIC GLOMERULONEPHRITIS  
(FOCAL "EMBOLIC" GLOMERULONEPHRITIS)



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FIG A Focal endocarditic glomerulonephritis in which the lesion is made up of a cluster of necrotic glomerular capillaries with fibrinoid alteration of their walls and with partial secondary thrombosis of their lumens. The thrombosis is altogether secondary and may or may not be present. The fibrinoid necrosis of the capillary walls is the primary alteration. (From a case of subacute bacterial endocarditis.)

FIG C Acute exudative and proliferative glomerulonephritis of acute bacterial endocarditis. Focal endocarditic glomerulonephritis is responsible for about one third of the cases of uremia in subacute bacterial endocarditis.

FIG B Diabetic glomerulosclerosis which superficially is not difficult to distinguish. The argyrophilic pattern of each is altogether different (see plates 213 and 214).

FIG D Diabetic glomerulosclerosis which superficially is not difficult to distinguish. The argyrophilic pattern of each is altogether different (see plates 213 and 214).



FIGS A AND B Kidney of disseminated lupus erythematosus showing the hemorrhagic, mottled, and irregularly pitted appearance of the cortex



other than skin would very likely be present in the disseminated disease

### Heart

The most striking cardiac lesion in disseminated lupus erythematosus is an endocarditis that has been called Libman-Sacks disease, or atypical verrucous endocarditis. This lesion occurs in about 30 per cent of cases of the disseminated disease. Grossly the vegetations tend to be friable and uniform in size in a given case, but may vary in different cases from a lesion that is hardly visible to one 4-6 mm in amplitude. They have a peculiarity in their occasional but by no means invariable occurrence in unusual locations such as the pockets or angles of the valves. The remainder of the vegetation is found near the line of closure as in the other varieties of endocarditis.

Histologically, the lesions are usually recognizable particularly by the characteristic hematoxylin bodies which are present also in other organs, and the prominent fibrinoid degeneration of the endocardium of the valves and chamber walls (plate 95 A). The hematoxylin bodies are obviously compressed and distorted nuclear residues, so that it is hardly surprising that they contain desoxyribonucleic acid. An incidental bacterial endocarditis frequently complicates the specific lesion terminally (Klemperer et al.), because it offers a nutrient nidus for the growth of bacteria that happen to be in the blood stream (Allen and Sirote).

Other cardiac lesions of this disease include a characteristic fibrinoid degeneration of interstitial collagen of the myocardium and of the epicardium (plates 95 B, 96 A).

### Spleen

Another almost pathognomonic change in disseminated lupus erythematosus is the concentric lamination of rings of hard dense collagen about the central arterioles of the spleen (plate 94). This change represents a collagenization of the normal fine reticulum, and is rarely seen in a full-blown state in any other disease, although miniature forms have been noted. This form of collagenization is quite distinctive from the soft, acidophilic, fibrinoid change in the glomerular capillaries, or in the interstitium of the myocardium. The splenic change occurs in about 95 per cent of cases of disseminated lupus erythematosus.

### Lymph nodes

No specific lesion is present in the lymph nodes which may, however, show areas of necrosis of the type seen in serum sickness, other allergic states, and in some infectious diseases, such as typhus fevers (Allen and Spitz). Infrequently, laminations of collagen about arterioles are found resembling those of the spleen (plate 96 B).

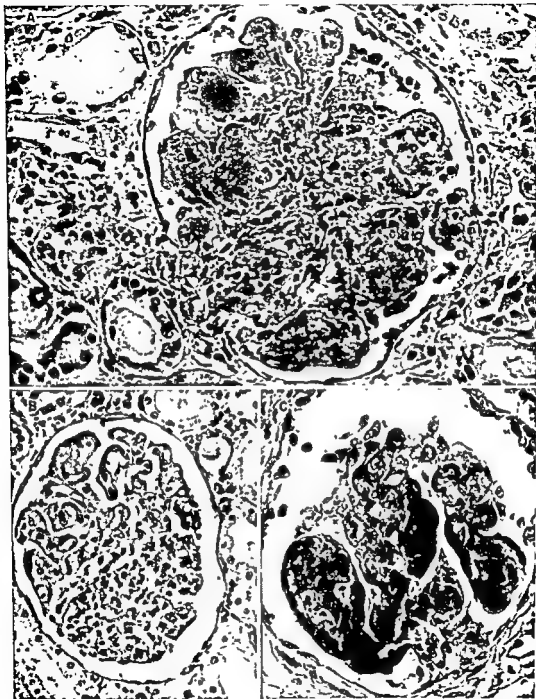
### Blood vessels

Blood vessels of approximately the caliber of renal interlobular arteries may be altered by varying degrees of fibrinoid alteration, sub-endothelial proliferation of fibroblasts, and perivascular collection of mononuclear cells so as to simulate periarteritis nodosa. These vascular changes may occur in a variety of organs including the choroid plexus of the brain. Impressive as the histologic change of an individual lesion may be, however, the fact is that many cases of disseminated lupus erythematosus occur without any such vascular

FIG A. Disseminated lupus erythematosus. Glomerulus shows characteristic fibrinoid swelling and degeneration of capillary walls, endothelial proliferation, exudation and karyorrhexis of leukocytes and beginning proliferation of capsular epithelium. The fibrinoid swelling is often so marked as to simulate thrombi.

FIG B "Wire-loop" lesion in upper half of photograph is almost pathognomonic of disseminated lupus erythematosus but may occasionally be seen in possibly related diseases, such as scleroderma, dermatomyositis and eclampsia. The "wire-loops" are focal, the remainder of the tuft shows the picture of acute exudative glomerulitis.

FIG C "Wire-loops" may swell and form vascular projections which have been mistaken for "hyaline thrombi." The lesion illustrated here is unusually marked, the more characteristic "wire-loops" are shown in figure B.



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lesions being demonstrable, at least in a routine number of sections. Moreover, in none of the 22 cases personally examined were there lesions of sufficient numbers of arteries in enough organs to begin to account for the clinical picture or the deranged physiology. The renal capillary damage is, of course, not included in the scope of this statement. It is this same cliché of *diffuse vascular disease* that has been used to explain the altered physiology of other diseases, for example, scrub typhus, even though arterial disease of the viscera is a rare histologic finding.

### *Miscellaneous*

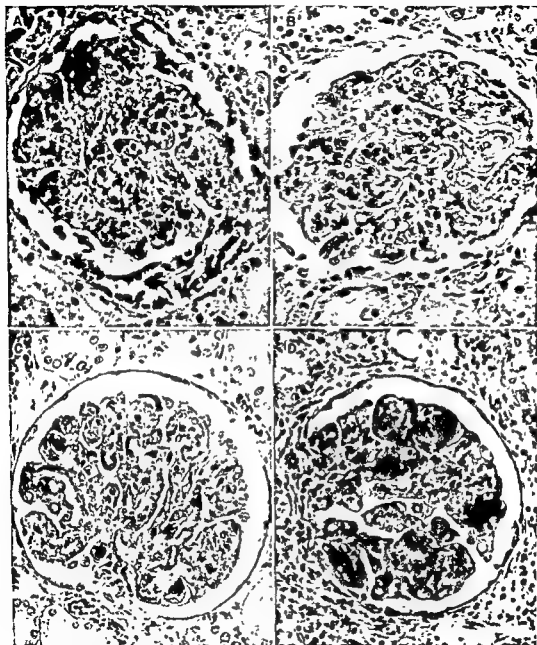
The serosal surfaces and areolar tissue may be the sites of fibrinoid alteration which may produce symptoms depending on the location. Focal inflammation of skeletal muscle is usually mild but at times may be intense. The routine sections of bone marrow do not show significant change, but recently a special "L.E." or Hargraves' cell has been described, which is found abundantly in the marrow, particularly in the severest stage of the disease. These cells may be found also in the peripheral blood in grave cases. The "L.E." cell itself is not a polymorphonuclear leukocyte as was originally and subsequently reported. The cell is mononuclear and resembles a lymphocyte with engulfed or accoladed polymorphonuclear leukocytes, often in rosette formation (plate 96 C, D). If the plasma from a patient with disseminated lupus erythematosus is added to the heparinized marrow from a normal person, or even from a dog, cells indistinguishable from "L.E." cells are produced. This procedure facilitates the finding of the cells. The phenomenon is attributed to specific gamma globulins within the blood, although thus far, a false positive has been noted in a case of multiple myeloma.

### *Common Denominators of Lupus Erythematosus, Scleroderma and Dermatomyositis*

The clinical and pathologic features of disseminated lupus erythematosus, scleroderma and dermatomyositis have been so intimately identified with each other that papers on therapy and pathology consider them inter-

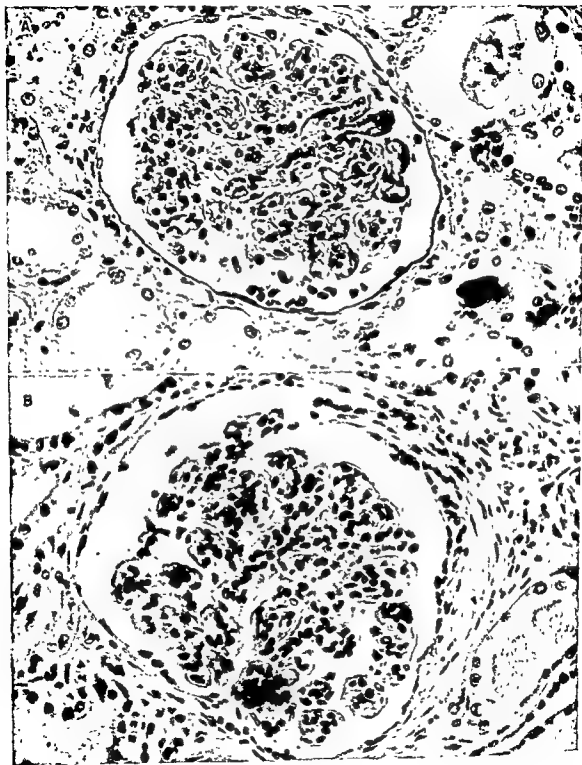
changeably in all basic respects. This point of view has developed from the assumption either that all three are diseases of collagen, or that all three are diffuse vascular diseases. Are such assumptions loose and convenient clichés or is there as much in common in the histologic picture of these diseases as is generally assumed? Actually, in scleroderma and disseminated lupus erythematosus, there are changes in the collagen, but the qualitative difference in the dense sclerosis of the cutis and of the submucosa of the esophagus and intestine of scleroderma (plate 97) from the fibrinoid degeneration of the serosa in lupus erythematosus warrants thinking in terms of basic dissimilarity. Although the characteristic "wire-loop" glomerular change has been observed in scleroderma (plate 98 A, B), it is a rare finding in this disease—about as rare as it is in the other exceptional cases in which it occurs. The peculiar edema and lamination of the intima of the renal interlobular arteries (plates 98 C, D, E, F) is an infrequent finding in scleroderma that resembles a change of malignant nephrosclerosis and does not suggest disseminated lupus erythematosus. The dense myocardial fibrosis of scleroderma is altogether different from the interstitial fibrinoid degeneration of the myocardium of disseminated lupus erythematosus. Finally, the mere fact of the existence of the combination of cutaneous and visceral collagenous changes in two diseases is not tantamount to establishing their essential identity, although the literature tends to indicate that it is.

The relationship of dermatomyositis to disseminated lupus erythematosus and scleroderma appears to have been built on an even more specious basis. In dermatomyositis, changes occur in the skin, muscle, nervous system, and, rarely, in the arteries. The cutaneous changes are altogether non-specific, in sharp contrast to the usually diagnostic changes of scleroderma and lupus erythematosus (plate 99 A). The myositis of dermatomyositis is often extensive, but, again, quite nonspecific (plate 99 B). Visceral vascular changes are, also, simply rare, although they do resemble the few visceral arterial lesions of lupus erythematosus. The neural changes, principally demyelination,



These photomicrographs show various degrees of glomerular alteration in disseminated lupus erythematosus including "wire loop" formation, verrucal swelling of walls of glomerular capillaries (so called "hyaline thrombi") and glomerulitis with karyorrhexis of endothelial cells

PLATE 92 DIFFERENTIAL HISTOLOGIC DIAGNOSIS OF LESIONS OF DISSEMINATED  
LUPUS ERYTHEMATOSUS



— of dig-  
h.

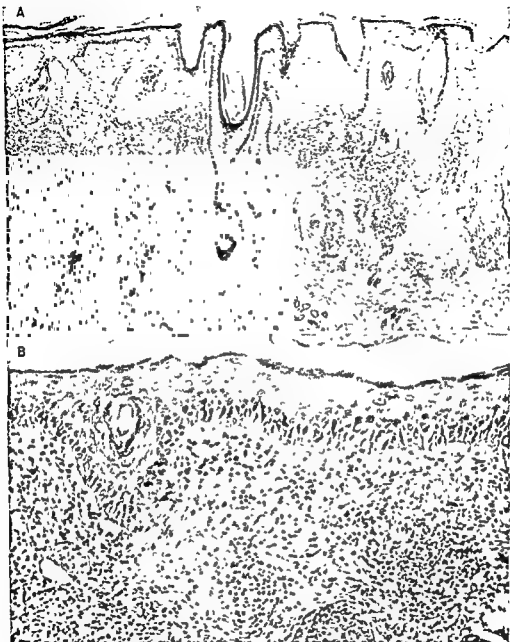


FIG A Skin in *chronic discoid lupus erythematosus* is diagnosable by histologic changes which consist of (1) compact masses of lymphocytes in mid-dermis or about appendages, (2) alternating epidermal acanthosis and atrophy, (3) keratotic plugs of follicles, (4) liquefaction degeneration of basilar layers, (5) subepidermal hyperemia, (6) focal parakeratosis

FIG B Skin in *acute disseminated lupus erythematosus* superimposed on discoid lupus erythematosus. The acute changes are indicated by the exaggerated liquefaction degeneration of the basilar layers, the prominence of the acidophilic cytoplasmic change at the junction of the epidermis and dermis, the fibrinoid degeneration of the collagen of the upper dermis, the nuclear distortion of subepidermal inflammatory cells and the suppurative hyperemia. Contrary to the general impression, degenerative or inflammatory vascular changes are usually absent in the skin in these cases

along with their antecedent phase and sequelae are the conditions of prime concern.

Hypertension and albuminuria together constitute definitely abnormal findings in pregnancy. Static hypertension and albuminuria, however, do not constitute preeclampsia. Generalized edema without hypertension is present in about 75 per cent of otherwise normal pregnant women (Fink). The edema, of itself, is rarely serious although it may be responsible for headaches, scotomas, and even convulsions and coma in isolated instances (Dexter and Weiss). The edema does not damage the fetus (Dexter and Weiss) and does not alone indicate a toxemia of pregnancy. It may be caused by hypoproteinemia, increased venous or capillary pressure, cardiac failure, anemia, vitamin B deficiency, myxedema, or excessive intake of sodium salts. An endocrine or possibly a renal factor may be at fault, but, nevertheless, edema as an isolated feature, is not of great significance during pregnancy. It is the association of edema with hypertension that begins to take on great importance.

#### *Preeclampsia and Eclampsia*

*Preeclampsia* occurs in the latter half of pregnancy, often at about the 34th week, it may occur also in the postpartum period. *Eclampsia* rarely begins later than 24 hours postpartum. This toxemia complicates about 1 in 139 to 1 in 620 pregnancies. It occurs much more often in primiparas than in multiparas. Probably the chief reasons for this selective incidence is the failure of survival of many of the patients as well as the discouragement of subsequent pregnancies. Preeclampsia or eclampsia may develop also in association with a hydatid mole (Pago).

Preeclampsia is characterized by hypertension and albuminuria (both above pre-pregnancy level), generalized edema, headaches, nausea and vomiting, vertigo, visual disturbances, drowsiness, twitchings, coma, and, in the eclamptic stages, convulsions. The eye-grounds are usually normal but papilledema, hemorrhages, exudates and even retinal detachment may occur. Levels of urea and non-protein nitrogen tend normally to be low in pregnancy and are usually within normal range

in toxemias of pregnancy. The resemblance of these signs and symptoms to those of severe, acute diffuse glomerulonephritis (especially of the membranous type) with hypertensive encephalopathy is obvious.

This symptom complex of preeclampsia or eclampsia may develop *de novo* during pregnancy or may be superimposed in patients with antedating hypertension and/or albuminuria on the basis of preexisting renal disease. In the past, such patients have been placed in the grouped labeled "low kidney reserve." Their renal lesions might be one of several: chronic glomerulonephritis, chronic pyelonephritis, benign or malignant nephrosclerosis, anomalies (e.g., polycystic kidneys) and probably other diseases that significantly compromise renal function prior to pregnancy. Many of these patients have an uneventful course although the incidence of stillbirths and abortions is high in this group. However, about 5 per cent of such patients develop preeclampsia (Dexter et al.). Rarely, renal diseases producing hypertension, such as acute diffuse glomerulonephritis, may first occur during pregnancy without leading to preeclampsia (Dexter et al.). Pyelonephritis initiated during pregnancy is a common evanescent and usually clinically unimportant condition (Robertson).

#### *Sequelae of Toxemias of Pregnancy*

In patients with preeclampsia without pre-existing hypertension, the infant mortality is about 5 per cent in the mild cases to 25 per cent in the severe ones (Peckham), in those with antecedent hypertension, the mortality is greater, ranging from 12 to 69 per cent (Corwin and Herrick). The earlier in pregnancy the preeclampsia develops, the greater is the infant mortality. The infants of preeclamptic and eclamptic mothers that survive the neonatal period suffer no demonstrable ill effects.

The maternal mortality from preeclampsia is about 1 per cent (Dieckmann and Brown), and from eclampsia, about 10 to 20 per cent (Stander). In these days of prenatal care, fortunately relatively few patients are permitted to deteriorate to the stage of eclampsia. The most frequent cause of death in eclampsia is left ventricular failure with pulmonary edema.

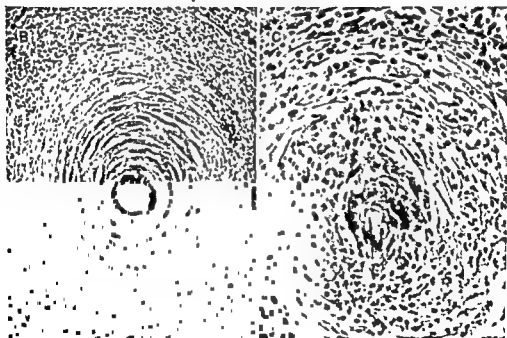


FIG. A Spleen in disseminated lupus erythematosus, the surface of which is speckled with periarteriolar fibrous tissue in follicles

FIG. B Concentric rings of periarteriolar fibrosis of malpighian corpuscles of spleen a very common finding in disseminated lupus erythematosus and uncommon in other diseases

FIG. C An early acute phase of the lesion pictured in figure B. In addition to the periarteriolar fibrosis, there is central fibroid degeneration and acute inflammation



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A

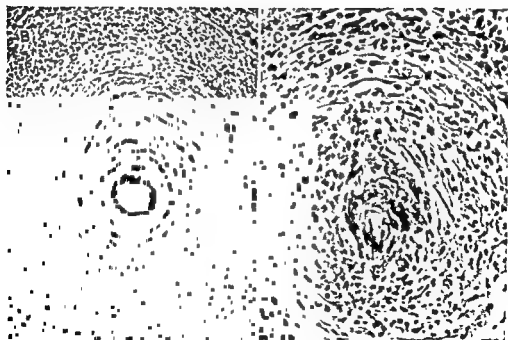


FIG. A Spleen in disseminated lupus erythematosus, the surface of which is speckled with periaarteriolar fibrous tissue in follicles

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FIG. C An early acute phase of the lesion pictured in figure B. In addition to the periaarteriolar fibrosis, there is central fibrinoid degeneration and acute inflammation



FIG. A Atypical verrucous endocarditis of disseminated lupus erythematosus "Hematoxylin bodies" are present (arrows) within the necrotic collagen of the verruca

FIG. B Interstitial fibrinoid myocarditis characteristic of disseminated lupus erythematosus Anitschkow myocytes, lymphocytes and a few polymorphonuclear leukocytes are intermingled among the long strands Distinction from Aschoff bodies is rarely difficult

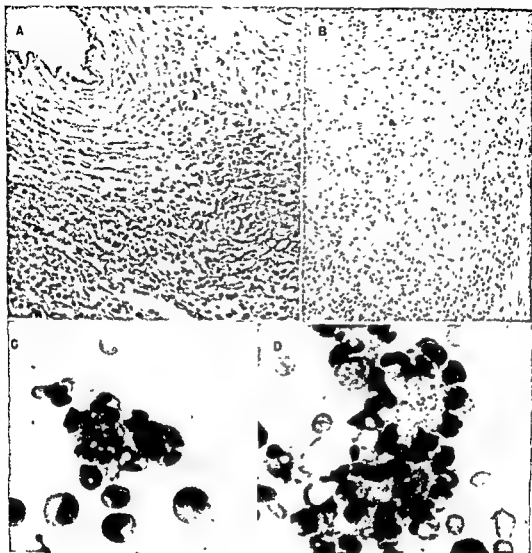


FIG. A. Epicarditis of disseminated lupus erythematosus with fibrinoid degeneration of fat.

FIG. B. Patchy necrosis of lymph node in disseminated lupus erythematosus similar to that seen in allergic reactions and in some infections such as scrub typhus.

FIGS. C AND D. "LE" cells from marrow. The "LE" cell of disseminated lupus erythematosus is practically pathognomonic of disseminated lupus erythematosus. It may be found in the peripheral blood, but is observed more easily in the marrow, especially of severely ill patients. The phenomenon of the "LE" cell may be produced by adding the patient's serum to heparinized marrow, even to marrow of a normal human or dog. The rosette of polymorphonuclear leukocytes about or within a mononuclear cell (probably lymphocyte) is especially characteristic.

Termination of the pregnancy is followed by rapid improvement in even the most desperate cases. Despite this improvement, however, hypertension tends to persist even after milder episodes of preeclampsia and is responsible for a high percentage of deaths in the following years (Herrick and Tillman). About 25 per cent of patients with toxemias of pregnancy without preexisting hypertension are left with a permanent postpartum hypertension, about the same percentage of hypertensive patients who develop the toxemia of pregnancy acquire an aggravated postpartum albuminuria and hypertension (Teel and Reid, Herrick and Tillman; Dieckmann and Brown). The vascular disease of essential hypertension appears to develop with greater frequency in patients with mild toxemias than in the eclamptic patients, as if the duration of the toxemia was more important than its severity in leading to this sequela. However, it should be mentioned in this summary of the sequelae of the toxemias of pregnancy that there exists a range of opinion on the subject, including the impression that practically no evidence of residual renal damage caused by the toxemia persists (Schmechel, Seitz).

#### *Pathologic Changes of the Toxemias of Pregnancy*

It is clear that renal disease may antedate the pregnancy and the toxemia, or it may be initiated during the pregnancy. In either case, the same clinical symptoms of preeclampsia or eclampsia may result. However, the renal changes will differ, and may be classified as follows:

Renal lesions of preeclampsia and eclampsia antedating pregnancy

Chronic glomerulonephritis (most common)

Chronic pyelonephritis

Benign and/or malignant nephrosclerosis

Various anomalies of the kidney with reduction of renal reserve

Renal lesions of preeclampsia and eclampsia initiated during pregnancy

FIG. A. Diffuse scleroderma of skin showing the dense, homogenized collagen of the cutis, the atrophy of the epidermis, and the melanotic pigmentation of its basal layer.

Bilateral cortical necrosis

Acute diffuse membranous glomerulonephritis (common)

Acute proliferative, exudative or necrotizing glomerulonephritis

Renal sequelae of preeclampsia and eclampsia

Chronic glomerulonephritis of various forms

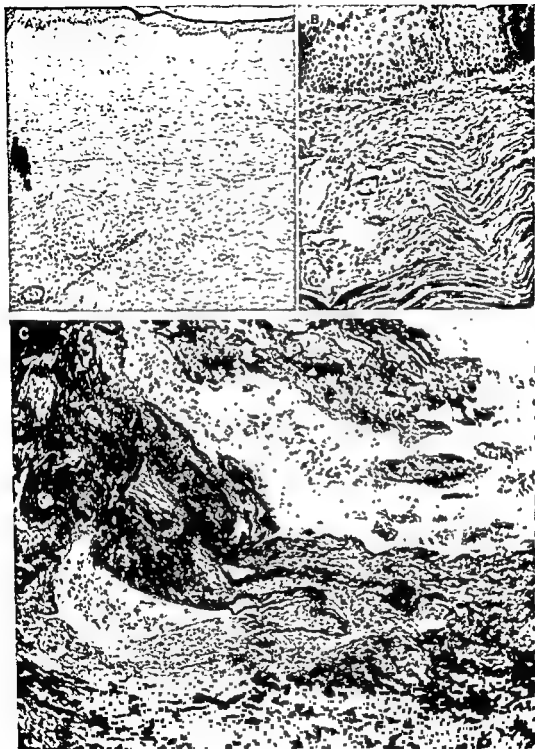
Benign and/or malignant nephrosclerosis

Of all the lesions listed, the acute diffuse membranous glomerulonephritis is of particular interest; the other lesions are discussed in their respective sections. It may be impossible to predict, from the immediate clinical picture, which variety of acute renal lesion will be found. Clinical data on the renal background of the patient are usually necessary for such diagnoses. On the other hand, there is a distinctive variety of membranous glomerulonephritis which, on histologic grounds, permits the diagnosis of toxemia of pregnancy to be made. This lesion was emphasized particularly by Lohlein and Fahr, and in this country by Bell, and is illustrated in plate 100. It consists of ischemic glomeruli with diffusely and uniformly thickened basement membranes, again, easily detected with routine stains, such as hematoxylin-eosin. Endothelial cells may or may not be increased and swollen. Occasionally, the membranous glomerulonephritis may be associated with focal fibrinoid, eosinophilic alteration of glomerular basement membranes so as to simulate the glomerular "wire-loop" change of disseminated lupus erythematosus (plate 102 B, C). Other vascular and interstitial changes are inconspicuous. The tubules are usually not seriously altered histologically; they may show hydropic, fatty, or hyaline degeneration and, infrequently, focal necrosis.

The proliferative, exudative and necrotizing forms of acute diffuse glomerulonephritis, or benign or malignant nephrosclerosis, or pyelonephritis may also occur with eclampsia and are not distinguishable from the corresponding lesions seen apart from pregnancy (plate 100).

FIG. B. Submucosal fibrosis of the esophagus in a case of scleroderma. The fibrosis may produce the clinical picture of peptic ulcer or esophageal obstruction.

FIG. C. Pulmonary cysts in scleroderma characterized by marked elastosis (Courtesy of S. Aronson).



(Legend on facing page)

A). Bilateral cortical necrosis is considered separately (page 472).

The changes in the liver in pre-eclampsia and eclampsia are diagnostic when they consist of: periportal and subcapsular hemorrhage, necrosis of hepatic cells at the periphery of the lobules, fibrinoid swelling of the basement membranes of Disse's space with marked hyperemia particularly in the periportal regions, and with occasional fatty infiltration of hepatic cells; and increased periportal lymphocytic reaction (plate 102 D). The hepatic change occurs in about 50 per cent of cases of eclampsia (Fahr) and may occur also in pre-eclampsia. The possibility that the hepatic changes may have a pathogenetic bearing on the renal lesions as in other hepatorenal diseases, cannot yet be dismissed.

The placenta in these toxemias tends to separate prematurely, to have an increased number and size of infarcts, and to show accelerated aging of the villi. Many observers attribute the toxemia of pregnancy to the placental infarcts and the toxic substances they cause to be liberated. The fact that signs and symptoms of the toxemia usually abate immediately after the pregnancy is terminated, suggests that toxic placental products may indeed spark the whole condition.

#### *Relationship of Pregnancy Glomerulonephritis to Chronic membranous Glomerulonephritis ("Lipoid Nephrosis")*

Acute membranous glomerulonephritis is found in the vast majority of pre-eclamptic and eclamptic patients. This lesion was found in 51 of 52 cases in Bell's series. This form of glomerulonephritis is histologically closely related

to chronic membranous glomerulonephritis and probably histologically identical with its acute stage. It will be recalled (page 154), that chronic membranous glomerulonephritis is characterized by the nephrotic syndrome, that is, by abundant albuminuria, marked edema and by hypoproteinemia with hypercholesterolemia, hypertension may or may not be present. Correspondingly, the clinical picture of pre-eclampsia with the acute membranous glomerulonephritis is similar in its basic respects to that of the nephrotic syndrome of relatively short duration. Hematuria is absent or mild.

Albuminuria, edema and hypoproteinemia are part of the symptom complex of the toxemia of pregnancy in which the acute membranous glomerulonephritis is found. The fact that the hypercholesterolemia is not especially marked over that of normal pregnancy, or that the degree of hypoproteinemia cannot always be directly correlated with degree of edema, or that hypertension occurs almost constantly, does not invalidate the essential thesis. In other words, the almost diagnostic acute membranous glomerulonephritis of pre-eclampsia and eclampsia—the glomerulonephritis described by Löhlein and later reemphasized by Bell—is really histologically and physiologically indistinguishable from the early stages of chronic membranous glomerulonephritis (i.e. the nephrotic form of glomerulonephritis or "lipoid nephrosis") occurring without pregnancy (plate 74 B). In both instances, the chief renal dysfunction is abnormal glomerular permeability to proteins, in both instances, renal failure is an inconspicuous feature. The chief point of divergence between the two entities is that the nephrotic type of syndrome of pre-eclampsia

FIGS A AND B "Wire-loop" thickening of glomerular capillaries in scleroderma. Such a picture is uncommon in cases of classical diffuse scleroderma in contrast to those with disseminated lupus erythematosus.

FIG C. Kidney in scleroderma showing marked narrowing of the lumen of an interlobular artery and "wire-loop" type of fibrinoid alteration of glomerular capillaries.

FIG E. Cellular swollen intima of an interlobular artery of kidney in scleroderma (Mallory-Heidenhain stain.)

FIG D. Cellular edematous intima of an interlobular artery of kidney in a case of scleroderma.

FIG F. Marked narrowing and fibrinoid necrosis of afferent arteriole of kidney in scleroderma. The vessels pictured in figures C, D, and E, are of themselves strongly suggestive of the diagnosis of scleroderma although they resemble the vessels of malignant nephrosclerosis.

PLATE 98. SCLERODERMA



(Legends on facing page)



generally clears if the pregnancy is survived; in the case of chronic membranous glomerulonephritis, the course is usually hopelessly progressive except for transient periods of remission. Without any question, termination of the pregnancy effects a restoration of the integrity of the swollen basement membranes of the glomerular capillaries. If in most cases the mechanism of this restitution were known, we should then have a significant clue to the mechanism of repair of the similarly altered glomerular capillaries of chronic membranous glomerulonephritis.

The more credible evidence indicates that at least hypertension persists in a large percentage of patients (25 per cent, Dexter and Weiss) who had not had this sign prior to the development of the toxemia of pregnancy. It appears that even though the permeable capillaries of the acute membranous glomerulonephritis of preeclampsia and eclampsia may heal, the effect of the hypertension and the toxemia may leave its permanent stamp on the afferent arterioles. It is believed that the residual afferent arteriosclerosis is the factor responsible for the persistence of the hypertension in these instances. (The matter of initiation of the hypertension is something else again and will not be belabored here. However, the recent suggestion of Hofbauer that hypertension in toxemia may be related to excessive activation of pituitary adrenocorticotrophic hormone might be mentioned in view of the role in the production of renal arteriosclerosis which Selye attributes to the adrenal corticoids.) The kidney illustrated in plate 102 F is an example of the effect of just such a sequence of events in an eclamptic patient with persistent and progressively mounting hypertension after gestation. At autopsy, no significant renal lesion beyond marked afferent arteriosclerosis was present, the glomerular tufts were remarkably intact.

## FUNCTIONAL GLOMERULAR PERMEABILITY

### *Benign Albuminuria*

There are many instances of individuals who, particularly near the age of puberty and during adolescence, excrete albumin for varying periods of time but do not have other evidence of organic renal disease. For example, 5 per cent of 50,000 otherwise healthy soldiers in training had albuminuria on arising, and after marching the incidence increased to from 7 to 14 per cent in a group of 200 (Maclean). This fact has long been known and corresponding figures of 4 per cent and 12 per cent were obtained by Leube in 1878 among soldiers on arising and after exercise. Because the albuminuria frequently is present only in the first urine passed in the morning, the condition has been referred to as cyclic albuminuria. However, the albuminuria in many cases is associated with a lordosis and so the name "orthostatic albuminuria" is applied. Even some of the instances of "cyclic" albuminuria are attributed to the assumption of the erect, lordotic posture upon getting out of bed, especially since the appearance of albuminuria could be delayed until evening by keeping the individual in bed all day.

Data on the percentage of cases of functional albuminuria in which posture is a factor vary considerably with the observer. According to some, all cases are related to posture; in direct contradiction, others have found that lordosis played no part in the functional albuminuria of a large group. The over-all evaluation of the experience with this condition leads to the conclusion that posture does play a role in the albuminuria in a high percentage of cases. The means by which the effect of changes in posture is detected appears to account for much of the discrepancy in the data.

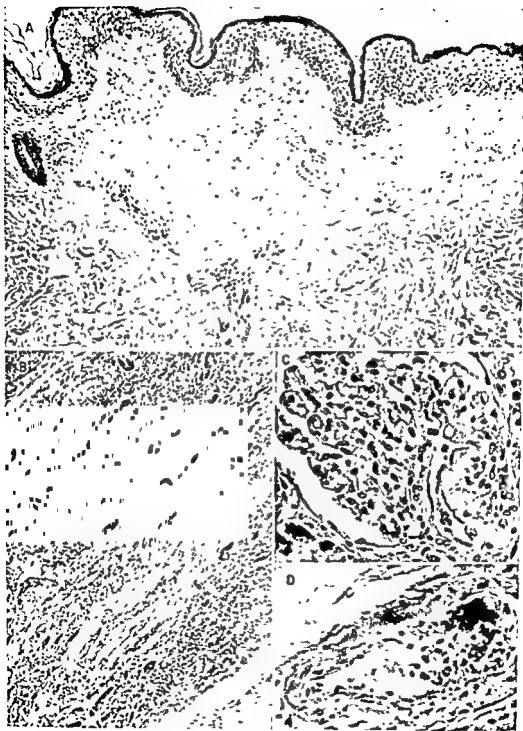
The total amount of protein lost in the urine

FIG A Skin in dermatomyositis almost always presents a non-specific histologic picture. Liquefaction degeneration, subepidermal edema and perivascular inflammation are usually observed in the degree shown here.

FIG B Myositis of dermatomyositis with atrophy of muscle fibers and infiltration of lymphocytes, histiocytes and scattered polymorphonuclear leukocytes.

FIG C Acute focal glomerulitis from a case of dermatomyositis with thrombosis of an afferent arteriole.

FIG D Fibrosed arteritis (pericardial) in case of dermatomyositis.



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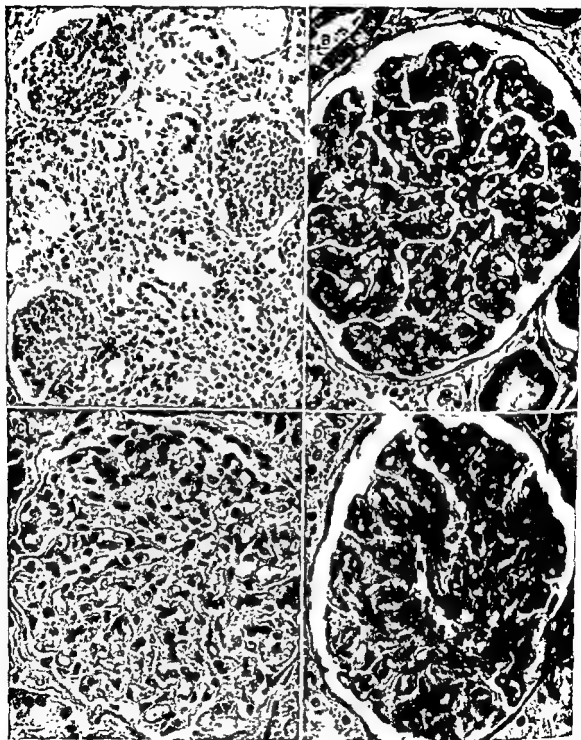


FIG A *Acute proliferative glomerulonephritis* associated with clinical eclampsia. This patient was 33 years old and in her last month of pregnancy (A F I P Acc 100491)

FIG C *Acute membranous glomerulonephritis* of eclampsia showing glomerular ischemia, decreased cellularity and membranous thickening of the capillary walls intermediate in quality between those of

FIG B *Acute membranous glomerulonephritis* of eclampsia with ischemia, and granular disintegration of some of the capillary walls

FIG D *Acute membranous glomerulonephritis* of eclampsia. This firm appearing thickening of the basement membrane is more nearly the standard prototype of glomerular change occurring in eclampsia.



FIG. A. Acute membranous glomerulonephritis of eclampsia with glomerular ischemia, marked focal fibrinoid alteration of glomerular capillary walls, and thrombosis of the afferent arteriole and glomerular capillaries.

FIG. B. Lower magnification of kidney of figure A showing fibrinoid necrosis of basement membranes of glomerular capillaries, thrombosis of their lumens and hyaline degeneration of proximal convoluted tubules with actual necrosis of epithelium of proximal convoluted tubules.

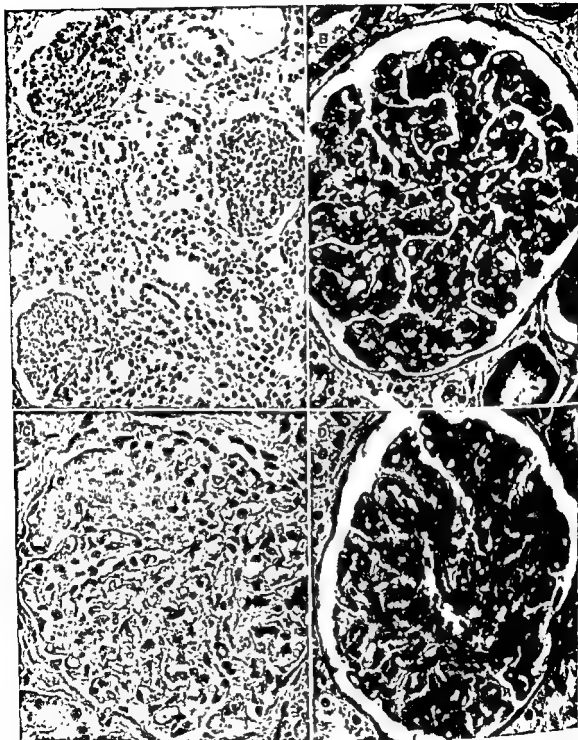


FIG. A. Acute proliferative glomerulonephritis associated with clinical eclampsia. This patient was 33 years old and in her last month of pregnancy. (A.F.I.P. Acc 100191)

FIG. C. Acute membranous glomerulonephritis of eclampsia showing glomerular ischemia, decreased cellularity and membranous thickening of the capillary walls intermediate in quality between those of figure B and figure D.

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FIG. B. Lower magnification of kidney of figure A showing fibrinoid necrosis of basement membranes of glomerular capillaries, thrombosis of their lumens and hyaline, hyaline droplet degeneration with actual necrosis of epithelium of proximal convoluted tubules.

PLATE 100. ACUTE GLOMERULONEPHRITIS IN ECLAMPSIA

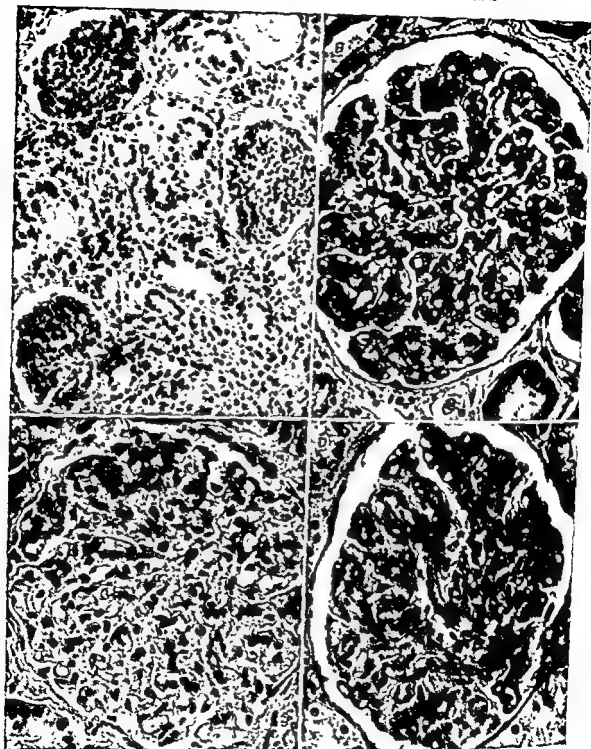


FIG. A. Acute proliferative glomerulonephritis associated with clinical eclampsia. This patient was 16 years old and in her last month of pregnancy. (AFIP Acc 100191)

FIG. C. Acute membranous glomerulonephritis of eclampsia showing glomerular ischemia, decreased cellularity and membranous thickening of the capillary walls intermediate in quality between those of

FIG. B. Acute membranous glomerulonephritis of eclampsia with ischemia, and granular disintegration of some of the capillary walls.

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FIG. A. *Acute membranous glomerulonephritis of eclampsia with glomerular ischemia, marked focal fibrinoid alteration of glomerular capillary walls, and thrombosis of the afferent arteriole and glomerular capillaries*

FIG. B. *Lower magnification of kidney of figure A showing fibrinoid necrosis of basement membranes of glomerular capillaries, thrombosis of their lumens and hyaline droplet degeneration with actual necrosis of epithelium of proximal convoluted tubules*



is not of a significance to be reflected in the lowering of the total blood level. The albuminuria rarely exceeds 0.2 to 0.3 per cent. However, as much as 3 grams of protein have been excreted in 24 hours by presumably healthy young adults (Peters and Van Slyke). Obviously, such a finding calls for extreme care and judgment in ruling out organic renal disease. The urinary protein consists of serum albumin as well as euglobulin, and the ratio of albumin to globulin (2 to 1) is considerably lower than it usually is in organic renal disease (Wallis), where it is of the order of 5-10 to 1.

The albuminuria is often constant but some cases show great irregularity in the periodicity of the albuminuria. The albuminuria may not be the only finding in the urine, small numbers of hyaline and granular casts, and even a few red blood cells may be present. At the height of the proteinuria, there may be oliguria. The standard tests for renal function, however, disclose no impairment.

#### *Pathogenesis*

If proteinuria, which often is the first indication of severe renal disease, is of no harmful significance, then what is its mechanism? In many cases, probably in the great majority, the excessive release of protein into the urine is related to posture or lordosis. Lordosis may affect a proteinuria by virtue of the position of the left renal vein which lies immediately anterior to the aorta, the right renal vein lies free of the aorta. It is assumed that the lordosis, by increasing the convexity of the aorta, exerts a transmitted pressure on the compressible left renal vein in contact with its anterior surface. The resulting increased venous pressure results in proteinuria. Occlusion of the renal vein is known to produce albuminuria and indeed,

cases of the nephrotic syndrome have resulted from thrombotic occlusion of the main renal veins, as previously indicated. Moreover, albuminuria, from passive congestion secondary to cardiac failure is a well recognized phenomenon. In orthostatic albuminuria, the protein has been found to come from the left kidney only (Himmán), that is, the kidney of which the renal vein is likely to be compressed by lordosis.

Those instances of benign albuminuria that cannot be related to posture are difficult to explain. Focal infection has been considered responsible for the glomerular permeability in some cases, and for this reason a few observers advise that serious efforts be made to remove such foci, even the less overt ones. Undoubtedly, scattered examples of nonspecific focal glomerulonephritis may masquerade as benign or orthostatic albuminuria, but such instances are not numerous. The relationship of benign albuminuria to exercise, emotional reactions or exposure to cold suggests an increased glomerular permeability, due probably to sudden relative glomerular ischemia or glomerular stasis. Marked but transitory albuminuria has occasionally followed the administration of vaccines, for example, yellow fever vaccines. The association of the proteinuria with growth and puberty is still to be explained.

#### *Diagnosis*

The importance of differentiating this "benign albuminuria," a term suggested by Fishberg, from the albuminuria secondary to organic renal disease is as obvious as it may be difficult. The absence of hypertension, edema, appreciably abnormal urinary sediment, renal dysfunction as measured by standard tests, retinopathy, and of changes in the level of protein and other blood constituents, favors

FIG A Acute membranous glomerulonephritis of eclampsia (Mallory-Heidenhain stain)

FIG B Lupus erythematosus-like lesion in acute membranous glomerulonephritis of eclampsia

FIG C Simulation of "wire-loops" of disseminated lupus erythematosus as marked in this instance of acute membranous glomerulonephritis of eclampsia

FIG D Later in eclampsia showing the characteristic periportal hemorrhage and necrosis, and thrombosis of sinusoids

FIG E Residuum of eclampsia at the age of 35 followed by persistent and progressively increasing hypertension to 200/100 over the next 13 years. The only significant renal change is marked afferent arteriosclerosis as shown here

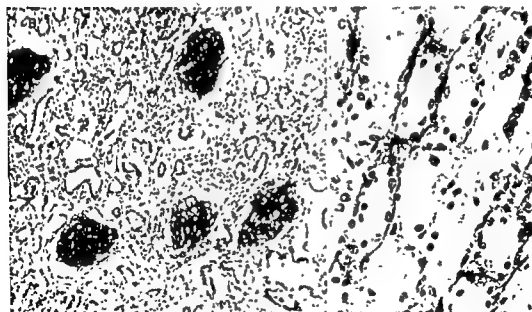


FIG. A. Argyrosis of kidney. Careful examination reveals black spots of impregnated glomeruli and pyramids darkened by deposits of silver.

FIG. B. Glomerular argyrosis from a patient who was treated with a solution of silver nitrate administered orally for a gastric ulcer.

FIG. C. Argyrosis with granules of silver adsorbed onto peritubular basement membranes.



FIG A *Argyrosis of basement membranes of medullary tubules due to silver medication (unstained section)*

FIG B *Glomerular argyrosis due to silver medication. Glomerular (or tubular) argyrosis apparently effects remarkably little renal dysfunction.*

FIG C *Normal argyrophilia of basement membranes of glomerular capillaries and tubules as demonstrated by modified Belschowsky's silver stain*

the diagnosis of benign albuminuria. Moreover, the relationship of albuminuria to posture is additional evidence of this condition, but it must be remembered that albuminuria secondary to organic renal lesions may be aggravated by postural changes. However, in benign orthostatic albuminuria, ureteral catheterization reveals that the albumin comes only from the left kidney. Perhaps the most relevant diagnostic problem is the differentiation of benign albuminuria from chronic glomerulonephritis of the nephrotic type. This differentiation may be made as a rule by the absence of edema, hypoproteinemia and hypercholesterolemia, as well as the absence of birefringent lipid

in the urine. Furthermore, the albuminuria leading to the nephrotic syndrome must be abundant and protracted, a situation that rarely is found in benign albuminuria.

### Prognosis

Benign albuminuria eventually clears spontaneously, sometimes at puberty, at other times it may last as long as 30 years (Fox). There is no way to predict its duration. Apparently, the albuminuria does not predispose an individual to organic renal disease. Treatment of the albuminuria *per se* is generally not worthwhile, and may focus undue attention on an innocuous urinary finding.

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FIG. A. Argyrosis of basement membranes of medullary tubules due to silver medication (unstained section)

FIG. B. Glomerular argyrosis due to silver medication. Glomerular (or tubular) argyrosis apparently effects remarkably little renal dysfunction

FIG. C. Normal argyrophilia of basement membranes of glomerular capillaries and tubules as demonstrated by modified Bielschowsky's silver stain

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# 7. Diseases of the Tubules

## CLASSIFICATION OF DISEASES OF THE TUBULES

- Proximal nephron nephrosis
  - Osmotic
  - Hyaline granule
  - Fat
  - Mercury
  - Potassium dichromate
  - Potassium chlorate
  - Ethylene glycol
  - Diethylene glycol
  - Bismuth
  - Hemosiderosis
    - Marchiafava-Micheli syndrome
    - Favism
    - March hemoglobinuria
    - Cold hemoglobinuria
- Proximal and distal nephron nephrosis
  - Hemoglobinuric ("lower nephron") nephrosis
  - Cholemic
    - Hydroquinone-pyrogallol acid
    - Sulfonamide
    - von Gierke's disease
- Distal nephron nephrosis
  - Myeloma
  - Gout
  - Uric acid "infarct"
  - "Inclusion Disease"
- Parenchymal nephrosclerosis

### OSMOTIC NEPHROSIS\*

In the years around 1940, hypertonic (50 per cent) sucrose, the disaccharide of glucose and fructose, was used extensively to combat cerebral or generalized edema (Jackson et al.,

Murphy et al.). However, its use was soon appreciably discouraged by the publication of reports of rather striking swelling of the renal tubular epithelium produced by the sucrose (Lindberg, Anderson). The histologic change in the epithelium was so prominent that the equivocal nature or complete lack of evidence of renal dysfunction with moderate doses at proper intervals was generally disregarded. Actually, most of these data were available in 1906 (Lamy et al.) and re-emphasized in 1933 when Helmholtz reported the effects of hypertonic sucrose in rabbits and in one human case. He subsequently observed rather similar qualitative changes with hypertonic glucose, sorbitol, sodium sulfate and urea. Phenolsulfonphthalein excretion is diminished in rabbits given excessive doses of sucrose at relatively close intervals (Helmholtz). However, these rabbits, weighing only 4 to 8 pounds received as much sucrose as would be given therapeutically to an adult weighing about 150 pounds. The overall evidence is that the administration of sucrose in proper doses, in the absence of severe dehydration, is a safe procedure as far as renal function is concerned.

### Histologic Appearance

The lesions produced by hypertonic sucrose (osmotic nephrosis) are confined almost exclusively to the proximal portion of the nephron including the descending limb of the loop of Henle. The lesion consists of a bland swelling of the epithelium by a sieve-like trelis of vacuoles, diffusely and regularly distributed throughout the cells favoring no one portion of the cell over any other. If only a single, extensively involved cell were examined, the vacuolization would be indistinguishable from that produced by diffusely dispersed lipid as in the nephrotic phase of chronic glomerulonephritis, that is, lobular or membranous glomerulonephritis. With special stains, it is discovered that these vacuoles contain neither fat nor glycogen, but are *hydropic*, in other words, they contain at least no stainable constituent. In routine

\* Some writers object to the use of *nephrosis* on the ground that the suffix "*osis*" means "abundance of," and therefore suggest the substitution of "*nephropathy*" for "*nephrosis*." It is not especially clear why the words *oedema*, *thrombosis* and *psychosis* are not found just as inadequate. In point of fact, "*osis*," as has been indicated previously (Am J Path 20: 1040, 1944), signifies either "an abnormal or diseased condition" or "a physiological increase" (Webster's International Dictionary, Second Edition, unabridged). Hence, "*nephrosis*" means disease of the kidney. By virtue of long usage, rather than literal definition, it has come to indicate *tubular* disease. The term "*tubular nephritis*" is attractive and has many advocates but it has the disadvantages of inaccuracy in its application to noninflammatory tubular lesions, and of some unwieldiness when the etiologic agent is appended.

sections, the *diffuseness* of the lesion throughout an individual proximal part of a nephron suggests the diagnosis of hydropic rather than lipid vacuolization. This is especially true if, in addition, most of the nephrons are involved, as they frequently are (plate 106). Despite the most conspicuous vacuolization, the brush border of the cells is usually intact. Often, beneath the cilia, the cytoplasm is least "vacuolated" and there may be a rim of hyaline granules as if displaced to the luminal border of the cell.

Actually, when studied under high magnification, the spaces that are loosely called "vacuoles" appear to represent collections of intracytoplasmic fluid that have been collected into the cell and have separated the normal granules so as to simulate vacuoles (plate 106 B). The impression that these are true vacuoles surrounded by a membrane in the morphologic sense of contractile vacuoles of paramecia or even of a lipid vacuole is, therefore, not substantiated by detailed histologic examination. The cytologic details are more in harmony with the conviction that the fluid, imbibed by the cell subjected to the hypertonic sucrose, elbows apart the ordinary cytoplasmic acidophilic granules readily visible in compact form in normal epithelium of proximal tubules. These lesions, with rare exceptions (plate 106 B) are entirely reversible.

The lumens of the proximal tubules may appear appreciably narrowed in cases with the more conspicuous lesions. However, Bowman's spaces are not significantly dilated and it is questioned if this apparent histologic compromise of the tubular lumen by the swollen tubular cells is of physiologic significance. This epithelial swelling begins about an hour after the hypertonic sucrose is administered, reaches its

maximum in 48 hours, and disappears in about 15 days (Helmholz).

It is of interest to note that loops of distal convoluted tubules in immediate juxtaposition to severely involved proximal tubules usually show no change. Occasionally, mild vacuolization in these distal tubules is seen, but may be easily overlooked because of the sharp quantitative contrast to the change in the proximal tubules.

Hypertonic sucrose may similarly alter the parietal epithelium of Bowman's capsule but otherwise does not affect the glomeruli, vessels, or interstitium of the normal kidney. Its effect on the interstitial edema of the kidney has not been satisfactorily demonstrated.

#### *Other Modes of Production of Osmotic Nephrosis*

This same type of vacuolization may be produced by other sugars in hypertonic solutions, such as 50 per cent xylose and 20 per cent inulin (plate 109, 110). We have noted it also with a variety of other hypertonic solutions, including 30 per cent acacia and 15 per cent creatinine, with subcutaneous and intraperitoneal injections of 50 per cent sucrose, and with the intravenous inoculation of 50 per cent sucrose as well as 50 per cent glucose in phloridized animals (plate 110 A). Moreover, we have observed the vacuoles after large amounts of isotonic sucrose had been administered intravenously. Wilmer, too, found that the epithelial vacuolization in rabbits produced by the intraperitoneal or subcutaneous injection of sucrose was not prevented by phloridzin. He made the interesting observation that intraperitoneal hypertonic (50 per cent) sucrose resulted in the vacuolar change in the pregnant rat but not in the fetus. We have, however, observed this type of vacuolization in the kidneys of newborn

FIG A Osmotic nephrosis (produced by 150 cc of 50 per cent sucrose solution given intravenously over a three day period) characterized by reversible vacuolated, hydropic swelling of epithelium principally of proximal convoluted tubules. Hyaline droplets are present in many tubules and represents intrinsic alteration of epithelial cytoplasm rather than absorbed protein

FIG B Changes identical with sucrose nephrosis can be caused by other hypertonic solutions including 10 per cent dextrose as in this case. The epithelial degeneration present in one tubule in above photograph is uncommon (Fat and glycogen stains are negative)

FIG C Changes of the sucrose type of nephrosis were produced in this kidney from a 7 day old infant by 1 1/2 ounces of 5 per cent glucose given orally and an infusion of 30 cc of 5 per cent glucose



(Legends on facing page.)

infants (plate 110 D) Intraperitoneal injection of hypertonic sucrose in the aglomerular toadfish does not produce the tubular change (Wilmer) Ligation of the ureter does not prevent the formation of sucrose vacuolization, in contrast to the protection afforded against poisoning by mercury bichloride and uranium nitrate by ureteral ligation Hayman and Hartman observed transient hyperlipemia in animals after the administration of hypertonic sucrose Incidentally, the coarse large irregular type of hydropic vacuolization of the proximal tubular epithelium found occasionally in dysentery (Jaffé and Sternberg), cholemic nephrosis and ulcerative colitis (Jensen, et al, Kulka et al) (plate 108 B) is morphologically distinguishable from that of osmotic nephrosis

### *Physiologic Pathology*

The interpretation of these facts is that many compounds may produce a hydropic vacuolization of the proximal tubular epithelium if they are present in sufficient molar concentration in the lumen in this part of the nephron Hence, the term "osmotic nephrosis" is suggested. It is our belief that the intracytoplasmic "vacuoles" are the direct result of the disturbance in the normal oncotic relationships between the osmotic pressure of the tubular fluid and that of the fluid within the tubular epithelial cytoplasm Hypertonic sucrose disturbs this relationship and causes the cellular imbibition of fluid so as to separate the cellular granules into "vacuolar compartments" Sucrose happens to be a particularly effective agent for the produc-

tion of osmotic nephrosis because, unlike glucose, it is not metabolized and is excreted practically quantitatively within a short time, thereby exerting its maximal osmotic effect

Even though glucose is metabolized, if a sufficient concentration of it is delivered to the tubular lumens by means of infusions or abnormal metabolism, as in a patient with diabetes mellitus, osmotic nephrosis will result. And, to be sure, such vacuolization is commonly seen in diabetic patients and is misinterpreted as glycogenic vacuolization. The failure of these vacuoles to take the stain for glycogen is generally ignored and attributed to the type of fixative used, or, no special stain is done, and the hydropic vacuoles are dogmatically labeled glycogen notwithstanding the fact that glycogen vacuoles in diabetes mellitus occur not in the convoluted portion of the proximal tubules but characteristically in the loops of Henle. Similarly, and just as erroneously, the vacuoles that follow the administration of aeneis or gelatin are usually considered to be actual collections of these substances in the proximal tubular epithelium, whereas, they too are hydropic vacuoles of osmotic nephrosis. This vacuolization, incidentally, appears responsible for the gross renal enlargement observed after the administration of gelatin (Baxter and Cotzias).

### *Physiologic Implications of Osmotic Nephrosis*

The detail with which osmotic nephrosis has been outlined reflects the author's conviction that the phenomenon is of importance, not be-

**FIG A** Osmotic (sucrose) nephrosis in milder form. These vacuoles do not take the stain for fat or glycogen.

**FIG C** Osmotic nephrosis in a diabetic. Epithelial changes similar to those of sucrose nephrosis. These are hydropic changes apparently effected by osmotic relationships between lumen and tubular cells. Such lesions in diabetics are often erroneously dismissed as due to deposits of glycogen.

**FIG E** Fat nephrosis. Phosphorus poisoning with marked fatty vacuolization of epithelium of proximal convoluted tubules. This may be distinguished from the lesion of sucrose or oncotic nephrosis even in routine sections stained with hematoxylin-eosin.

**FIG B** Osmotic nephrosis. Changes produced by infusions of 10 per cent glucose. Negative for glycogen and fat. The brush border helps to identify the tubule as belonging to the proximal nephron.

**FIG D** Osmotic nephrosis. Hydropic vacuolization in proximal tubules in cholera identical with those of sucrose nephrosis and probably dependent on oncotic changes associated with severe diarrhea. This vacuolization is different from the coarse type also found in dysentery (Jaffé and Sternberg) and in ulcerative colitis (plate 108, figure B).

**FIG F** Fat nephrosis in proximal tubules in diabetes mellitus. This basal vacuolization is easily recognized as lipid even in such routine sections. A similar lesion occurs in other conditions, as in hepatitis due to carbon tetrachloride or chloroform.



(Legends on facing page)

cause of any impairment of renal function wrought by hypertonic solutions, but because of the normal physiologic implications. It is an importance inferred from the impression that if we knew the exact cytomorphology of the epithelial vacuolization, we should then have some information about normal renal function, and, undoubtedly, information, too, about vacuolization of cells in other tissues. In this latter regard, there is supporting evidence from Opie's experimental production, *in vitro*, of vacuolization of renal tubular epithelium placed in hypotonic solutions. The vacuolization simulates the sucrose lesions histologically. In other words, it appears that renal vacuolization is produced not by the presence of sucrose or other administered substances within the cell in the sense of lipid or glycogen vacuoles, but by the imbibition of fluid within the renal epithelial cells by virtue of the oncotic changes produced by sucrose, glucose, and even protein, in extravagant concentrations within the tubular lumens and/or capillaries. The fact that the solutions in Opie's experiments were hypotonic does not negate the thesis that these tubular epithelial changes are the result of osmotic influences. The difference is one of site of action rather than mechanism.

It is a reasonable premise, with the data at hand, that the mechanism of vacuolization due to hypertonic sucrose is essentially the same as that produced by other sugars. Inasmuch as the sucrose is eliminated practically quantitatively within 24 hours (Keith et al.) and inasmuch as the vacuolization persists for several days thereafter, it is obvious that the vacuoliza-

tion can hardly be the result of sucrose retention in the cells.

Second, it is generally conceded that phloridzin prevents the reabsorption of glucose by the renal tubules and a similar barrier appears to be effected against sucrose reabsorption. This conclusion is confirmed by the identical clearance of glucose and sucrose (and xylose) in phloridzinized dogs (Smith). Nevertheless, the osmotic nephrosis, or tubular epithelial vacuolization, occurs following the intravenous administration of hypertonic glucose or hypertonic sucrose in phloridzinized animals. Hence, the vacuolization is not the result of the intracellular accumulation of these hypertonic sugars which must exert their oncotic effects from a position outside the tubular cell, most likely the tubular lumen or possibly the peritubular capillaries.

Third, if the vacuolar lesions are dependent on an abnormally high concentration and effective osmotic pressure of a substance within the tubular lumens, why are the lesions more severe with 100 cc. of 50 per cent sucrose than with 100 cc. of 50 per cent glucose? As indicated, the reason is that the tendency of glucose to produce the lesion is appreciably neutralized by the facts that (1) much of the glucose is metabolized and hence not available to exert osmotic suction in the tubular lumen, and (2) the glucose, in much greater proportion than sucrose, is reabsorbed across the tubular epithelium, thereby accounting for the loss of an additional increment in the osmotic tension within the tubular lumen. Similarly, the reabsorption of 25 per cent xylose reduces the vacuologenic efficiency of xylose. The greater vacuolar effect

FIG. A. Fatty changes in proximal tubules in chronic membranous glomerulonephritis ("lipid nephrosis"). This diffuse distribution of lipid may be difficult or impossible to differentiate from osmotic nephrosis in routine sections.

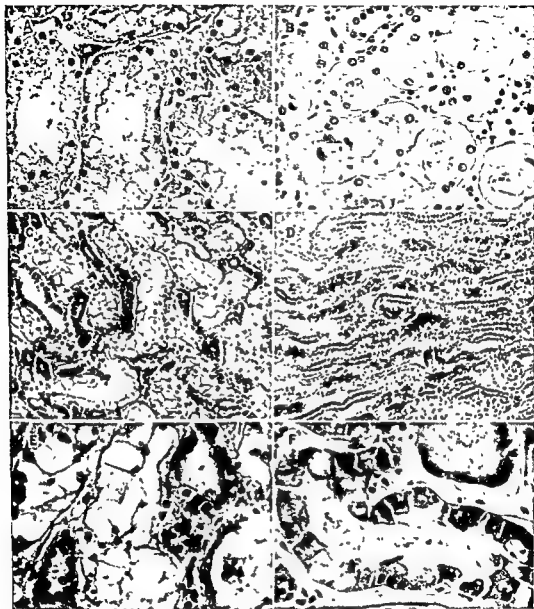
FIG. B. Gross vacuolization of the epithelium of the proximal nephron from a case of colonic carcinoma with diarrhea. Similar changes are noted in cases of ulcerative colitis and occasionally in cholemic nephrosis. Observed in 1918 by Jaffé and Sternberg.

FIGS. C AND D. Glycogen vacuoles (Armanni-Ebstein) in loops and limbs of Henle in severe diabetes mellitus. Figure D shows the positive stain for glycogen (black masses) in the vacuoles (Best's carmine).

FIG. E. Diethylene glycol nephrosis with a destructive clear vacuolization. The entire contents of many of these cells are cast off into the lumens. These vacuoles do not take the stain for fat or glycogen.

FIG. F. Cholemic nephrosis with a distinctive

PLATE 108. NEPHROSIS OF PROXIMAL NEPHRON: OSMOTIC NEPHROSIS  
(DIFFERENTIAL DIAGNOSIS)



(Legends on facing page.)



of sucrose as opposed to the equally nonmetabolized inulin, is accounted for by the enormously greater molecular weight of the latter (about 5000 for inulin versus 342 for sucrose) and hence the much lower osmotic pressure of inulin.

The conclusion therefore, is that the "vacuolar" lesion is produced by excessive concentration of sucrose, glucose, or, indeed, one of a great variety of substances, including urea, and sodium sulfate, within the proximal tubular lumen, and that this concentration results in imbibition of fluid, possibly from peritubular capillaries, into the epithelial cell with resultant temporary swelling. Moreover, it is clear that the abnormal tubular concentration for each substance need not be obtained by the intravenous injection of a hypertonic solution. The production of sucrose lesions by the intravenous injection of isotonic sucrose, the intraperitoneal and subcutaneous injections of hypertonic sucrose in rabbits (plate 110 B) and guinea pigs, as well as the injection of hypertonic sucrose into the lymph sacs of frogs, substantiates this point of view. In each of these instances, the sucrose is necessarily absorbed into the blood stream in isotonic concentrations. Therefore, the data focus again on the abnormally high concentration of the sucrose in the tubular fluid, rather than on its hypertonicity in the blood, as a cause of the epithelial swelling. To explain why this same type of vacuolization is not produced in the lower portions of the nephron, as in the collecting tubules, one must resort to the teleologic explanation that renal epithelium in this region is "accustomed" to hypertonic solutions. What actually enables these cells to withstand the oncotic pressure to which their more proximal counterparts are vulnerable is still to be learned. From the structural point of view, the cells of the proximal tubules, by virtue of their normal rodlets and fine, loose granules, in contrast to the cytoplasm of the more distal tubules, seem especially vulnerable to this type of change.

#### HYALINE GRANULE (COLLOID DROPLET) NEPHROSIS

##### *Relationship to proteinuria*

Although most observers assume that the glomerular filtrate is truly an ultrafiltrate of

the plasma, and, therefore, protein-free, there are others—and their numbers are increasing—(e.g., Addis, Oliver) who believe that normally during the course of the day, a minute amount of protein escapes into the glomerular filtrate and is then reabsorbed by the tubular epithelium. Actually this hypothesis is inferential and is not supported by the determination of the protein content made by the original direct measurements on aspirated glomerular filtrate (Wearn and Richards, Richards). It is effectively pointed out, however, that proteins seep through other capillaries, and that microchemical methods do not permit detection of less than 0.020 Gm. per cent of protein, which is assumed to be the order of seepage, and finally that if this amount did escape the glomerular capillaries, there would have to result an albuminuria of about 36 Gm. per day, instead of a normal of about 10 mg. (Addis). Therefore, practically all of the 36 Gm. of protein must be reabsorbed by tubular epithelium.

A significant part of the evidence for the capacity of the tubules to reabsorb protein is considered to be the hyaline granules found in clear cases of proteinuria. These granules are regarded as reabsorbed protein on evidence that is not altogether convincing. For a long time they were so regarded merely because they were associated with proteinuria, although some observers (Terbruggen) suggested that the granules consisted of protein in the process of being secreted into the tubular lumen by the epithelium. More recently, various proteins that had been coupled with red dye (disodium salt of 2-naphthol-3,3-disulfonic acid) were injected into animals, and colored granules were subsequently found in the proximal tubular epithelium (Smetana). It was therefore assumed that the colored intracytoplasmic granules represented the original protein, still coupled with dye, which was reabsorbed into the epithelium from the tubular lumen. This is a key assumption which lacks adequate proof. Similar colored "droplets" were noted when the proteins and dyes were injected separately (Oliver). Moreover, droplets of hemoglobin are said to have been noted in the proximal tubular epithelium (Rathert). The reabsorption of hemoglobin comprises an especially complicated situation made more complicated by the well

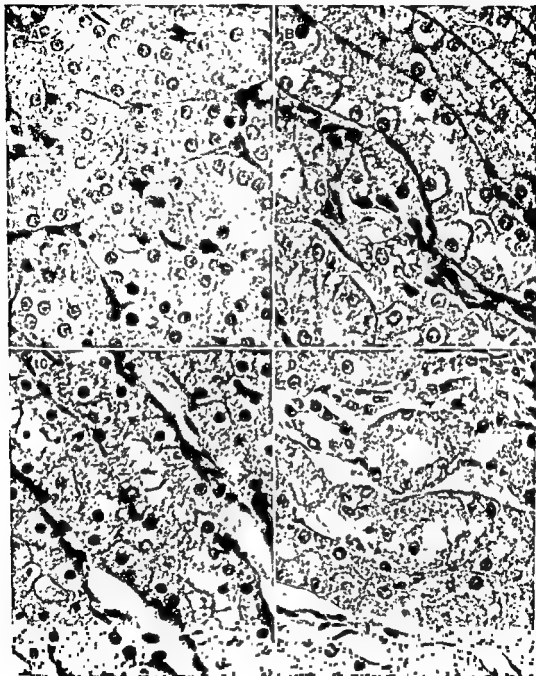


FIG A Control kidney from normal rabbit

FIGS B, C AND D illustrate osmotic nephrosis in rabbit given intravenous hypertonic injection of solutions of inulin (B), xylose (C) and urea (D)

known unreliability of the stains for hemoglobin in tissue, and by the presence of hemosiderin. It is of interest that in human cases of hemoglobinuric or myohemoglobinuric nephrosis, and after excretion of myohemoglobin in animals (Yuile, Gold and Hinds), droplets of hemoglobin are not observed in the proximal tubular epithelium.

#### *Intraepithelial origin of hyaline granules*

Nevertheless the evidence appears to us in favor of the view that the hyaline or colloid droplets, which are commonly seen in many renal diseases [such as, membranous or lobular glomerulonephritis ("lipoid nephrosis"), amyloidosis, malignant nephrosclerosis, and in instances of frank tubular degeneration from chemical poisons] are the result of an intrinsic intraepithelial alteration of the normal cytoplasmic granules. This subject and point of view were convincingly and authoritatively presented in 1914 by Volhard and Fahr. They concluded that these granules were evidence of cellular degeneration and that they were derived from normal cytoplasmic constituents which others had previously believed were the basilar Altman's granules. The observation of the various grades of severity of hyaline granular degeneration, from that in "lipoid nephrosis" to the extreme degree in necrotizing nephroses of potassium dichromate or diethylene glycol, makes no conclusion tenable other than that these acidophilic droplets constitute intracellular transformations of cytoplasmic structures rather than reabsorbed protein (plates 111, 112).

The original structures are the normal, fine, acidophilic granules and their underlying basilar rodlets. The droplets may be huge, especially at the luminal border, where they may be seen in the process of extrusion rather than in atrophy. The large extruded droplets are also found in the lumens of the tubules into which they have been sloughed; the large size of many of the granules makes their absorption by epithelial cells inconceivable. Moreover, the presence of these same granules in the parietal epithelial cells of Bowman's capsule (plate 112 D) can hardly be construed to indicate their origin from reabsorbed protein,

since no one would consider reabsorption of protein a function of these cells. It is pertinent that vital dye (trypan blue) injected by itself may also be found in the epithelium of Bowman's space (Suzuki) as well as in the epithelium of the proximal tubules.

#### *Pathogenesis*

What is the mechanism of the formation of these granules? In 1917, it was suggested (Allen) that the original granules of the cells of the proximal convoluted tubules become swollen because of local changes in osmotic pressure, so that fluid is imbibed by the granules. This explanation was based on the observation of these droplets in the proximal tubular cells after the administration of a variety of hypertonic solutions. Recently, Opie (1947) in a series of experiments, has produced similar changes in tubular epithelium of thin slices of kidney placed in hypotonic solutions and in distilled water. He estimates (Opie, 1930) that, in potassium chromate nephrosis, for example, the osmotic pressure of the epithelial cells falls to that of the surrounding medium and returns to the normal level with recovery. This kind of observation, which appears to have been neglected by those who believe the granules represent reabsorbed protein masses, is additional strong evidence for the oncotic origin of the hyaline or colloid droplets of the tubular epithelium. The fact that the number and size of granules decrease with increase in molecular weight of the protein (Oliver) further suggests the oncotic basis for their formation inasmuch as larger molecules exert less osmotic pressure than smaller ones. The observation that the droplets become colored by dye even when the dye and protein are given separately is interpreted by us to mean the dye colors the epithelial cytoplasm including the oncologically enlarged granules. It would seem altogether without basis to assume that the dye especially selected the droplets of "reabsorbed" protein. Moreover, the persistence of the colored granules in the renal epithelium for several weeks is not evidence that they represent reabsorbed protein inasmuch as Suzuki long ago (1912) showed that the dye administered by itself may be found as granules in the renal epithelium.

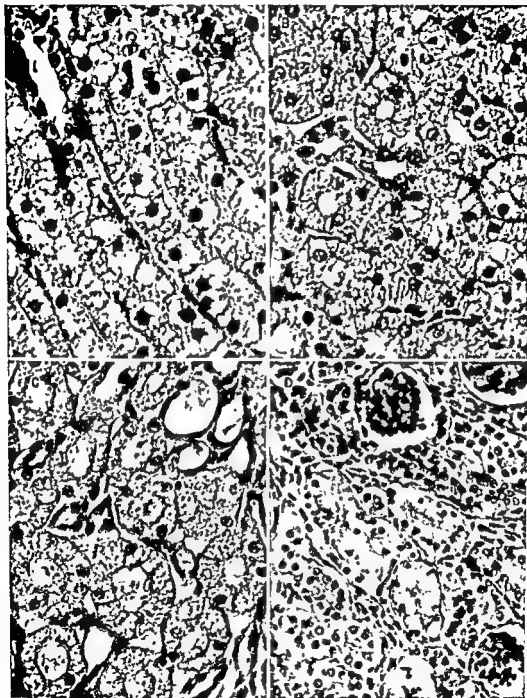


FIG A *Osmotic nephrosis in rabbit from hyper-tonic sucrose (30 cc, 50 per cent intravenously) and ploridzin*

FIG B *Osmotic nephrosis in rabbit from the subcutaneous injection of hyper-tonic sucrose*

FIG C *Osmotic nephrosis in rabbit from hyper-tonic solution of sodium sulfate (10 cc, 20 per cent, intravenously, sacrificed in 15 hours)*

FIG D *Osmotic nephrosis in stillborn infant*

three to four weeks later. In addition, it is known that the proteins hemoglobin (as opposed to hemosiderin) and myohemoglobin quickly disappear from the kidney after reabsorption (Xule, 1941), within days—not weeks.

Finally, if the hyaline droplets did in fact represent reabsorbed protein, it might be reasonably anticipated that there would be a positive correlation between the occurrence of such droplets and the presence of proteinuria. No such correlation exists (Rather<sup>4</sup>).

#### *Functional Disturbance from Hyaline Droplet Nephrosis*

It is stated that the hyaline droplets occur only in structurally undamaged epithelial cells inasmuch as they are not formed in regenerating epithelium, or in epithelium previously injured with uranium nitrate or bichloride of mercury (Oliver). On this basis, it has been concluded that the droplets "are not evidence of damage but proof of a certain functional and structural intactness" (Oliver).

It is entirely agreed that some vitality of the epithelial cell is essential for the appearance of the hyaline droplets. This is not so because the integrity of the cell is necessary for the reabsorption of protein, but rather because a necrotic cell, perhaps with ruptured cell membranes, is not capable of the osmotic reactions of the intact cell. Similarly, a regenerating cell of the proximal tubule is structurally and chemically (e.g., phosphatase content) a great deal different from the normal cell, and may appear as dissimilar from a cell of the proximal tubules as from a cell of the collecting tubules. It is for these reasons that hyaline droplets do not tend to form in previously severely altered cells. On the other hand, hyaline droplets usually represent a mild, reversible, osmotic reaction, but may constitute the initial phase of a necrotizing process. The evidence for this statement

may be observed, for example, in the various stages of degeneration of renal epithelium poisoned with potassium dichromate or diethylene glycol (plates 115, 119). Indeed, as already stated, Opie observed such granules in the epithelium of tubules exposed to dichromate, and concluded that there had been a marked reduction in the osmotic pressure of the epithelial cells. In other words, osmotic changes, in special instances, can be carried out to irreversible proportions, causing cellular rupture and death.

In summary, the hyaline droplets represent a variety of osmotic nephrosis. This is not to deny that protein is reabsorbed by the tubules. It is merely that the reabsorbed protein does not take the form of hyaline particles engulfed by the tubular epithelium from the glomerular filtrate.

#### FAT NEPHROSIS

The term *fat nephrosis* is used in contradistinction to *lipoid nephrosis*, to refer to the prominence of lipid in the epithelium of the proximal convoluted tubules in patients who do not have the nephrotic syndrome. Lipoid nephrosis has for a long time designated the clinical and histologic entities that are herein regarded as forms of glomerulonephritis with edema. It is felt that the clinically silent, reversible, purely tubular, histologic entity of fat nephrosis ought to be distinguished from lipoid nephrosis despite the use of possibly confusing terminology.

The histologic picture of fat nephrosis occurs in cases of phosphorus poisoning, in some cases of poisoning by carbon tetrachloride, chloroform, tetrachlorethane, chloral hydrate, bromoform, iodoform and in some cases of diabetes with hypercholesterolemia (plate 107). In the latter instance, there is usually evidence of severe diabetes as well; in phosphorus poison-

FIG. A Hyaline granules with great diversity of size in proximal convoluted tubules in a case of malignant nephrosclerosis. These "colloid droplets" result from swelling of intrinsic cytoplasmic granules rather than from reabsorbed protein.

FIG. B Hyaline granules in proximal convoluted tubules in case of sulfathiazole glomerulonephritis. These cells are obviously in various stages of degeneration.

FIG. C Hyaline granules in epithelium of proximal convoluted tubules in malignant nephrosclerosis.

PLATE 111. NEPHROSIS OF PROXIMAL NEPHRON: HYALINE (COLLOID)  
GRANULE NEPHROSIS



(Legends on facing page )

ing, there is generally equally prominent histologic evidence of fat in the liver, in the case of the volatile poisons, there is no direct correlation between the amount of fat in the liver and in the kidney.

✓ The renal lesion is characterized by more or less of a coalescence of basal vacuolization forming a fatty rim on the inner side of the tubular basement membrane. The vacuoles, which are generally separated by cytoplasmic septa, elevate, and partially surround the nuclei that are otherwise unchanged. The fat is confined strictly to the epithelium of the proximal tubules, including the convoluted portions, the descending limbs, and the loops of Henle. The lesion is diffuse, involving all of the nephrons. Fat nephrosis, unlike the so-called lipid nephrosis, is not accompanied by lipid deposits in the glomeruli, vessels, or interstitium.

The fatty change that is associated with lobular or membranous glomerulonephritis (clinical "lipoid nephrosis") involves the same portions of the nephron, but the involvement tends to be irregular. In addition, the lipid is not basal in location but is distributed diffusely through the cell in a pattern of lattice-work. The diffuse cytoplasmic lipid vacuolization is characteristic also of the fatty changes in the proximal tubules in amyloidosis, atrophic nephrosclerotic kidneys and particularly in the kidneys of diabetic glomerulosclerosis (plate 240). In the latter kidneys, in amyloidosis, and in those with lobular or membranous glomerulonephritis, the fat is, in part, anisotropic.

### MERCURIAL NEPHROSIS

Mercuric chloride (mercury bichloride, corrosive sublimate,  $HgCl_2$ ) is the compound responsible for most of the deaths from mercury. The deaths are caused by accidental or suicidal ingestion or by the use of the bichloride as a vaginal douche or as an abortifacient. Cases of poisoning have been reported following the use of solutions of mercuric chloride in the irrigation of the field of a surgical operation, or as a cutaneous fungicidal agent. The minimal lethal dose for humans is difficult to estimate but 3 grains have caused death (Gonzales et al.). Whether or not renal damage was present in this latter case is not indicated. In other series

(Peters et al.) patients recovered after taking at least 15 grains; none survived who had taken more than 4 tablets (30 grains or 2 Gm.). In dogs, 5 mg./Kg. intravenously invariably produced anuria and death (Sansum) and 20 mg./Kg. by stomach was required for constant fatality (Haskell et al.). The human dose corresponding to the peroral lethal dose of dogs would be about 1.4 Gm. for a 70 Kg. adult, agreeing with the actual observations of most series.

Mercurial compounds other than mercuric chloride may be toxic. The mercuric are more poisonous than the mercurous salts because of the greater solubility of the former. The mercuric salts include, in addition to the bichloride, mercuric iodide, mercuric oxide, mercurammonium chloride, mercuric salicylate, and mercuric cyanide. The mercurous salts are mercurous chloride (calomel), mercurous iodide and mercurous oxide. Practically all of these compounds have caused fatalities (Gonzales et al.). Apparently, in such instances, the mercurous salts are converted into mercuric form. The organic mercurial compounds such as Salyrgan, Novarsal and Mercurochrome have also caused death on occasion. The first two, Salyrgan and Novarsal, have resulted in sudden death during their administration intravenously as diuretics; no renal lesion attributed to their use has been found in these cases. Mercurochrome has in the past been used intravenously as a bactericidal drug and has resulted in death with findings similar to those of poisoning by mercuric chloride (St. George).

### Clinical Symptoms

The clinical picture of mercury poisoning is characterized by stomatitis, abdominal pain and bloody, mucous vomitus if the poison has been ingested. Shortly afterwards, diarrhea and severe tenesmus appear owing to the development of a hemorrhagic colitis. Death may occur in shock within the first 24 hours. If this period is survived, anuria or oliguria with mild to moderate albuminuria and scanty hematuria ensue. Glycosuria may also be present. The urine is of low specific gravity even when oliguria is present; the urine contains hyaline, granular, and epithelial casts and granular epi-

PLATE 112 NEPHROSIS OF PROXIMAL NEPHRON: HYALINE (COLLOID)  
GRANULE NEPHROSIS

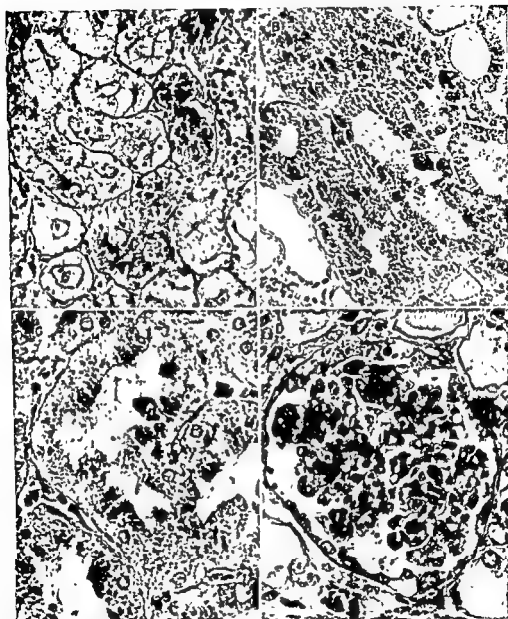


FIG A Osmotic (sucrose) nephrosis with hyaline granules in less severely altered cells

FIG C Hyaline granules resulting from intrinsic cytoplasmic alteration in a case of malignant nephrosclerosis

FIG B Hyaline granules in intrinsically altered epithelium of proximal convoluted tubule in a case of chronic glomerulonephritis

FIG D Glomerular epithelial cells with hyaline granules identical with those in figures A, B, and C. Obviously these granules in this location can not be attributed to reabsorbed protein



thelial debris. If the diminution in urinary output persists, stupor, coma and uremia set in. In the anuric stage, hypertension may occur although it is often absent. The level of blood chlorides may be markedly reduced. Death in this stage usually occurs from renal insufficiency associated with circulatory collapse although occasionally the colitis may be the major factor. Treatment with BAL (British Anti-Lewisite; 2,3-dimercaptopropanol) is remarkably effective if instituted in the first few hours following poisoning. BAL is presumed to act by successfully competing for combination with mercury against the sulfhydryl groups which are essential for the integrity of the cells. Death after renal insufficiency sets in is said to occur in about 12 per cent of cases.

### Pathology

#### Gross appearance

The kidneys are enlarged and soft. In the early and later stages they may be markedly congested, in the intermediate phase, approximately the first week, they may be a pallid grey.

#### Histologic appearance

The most conspicuous change in the kidneys affected by mercury bichloride is the degeneration, regeneration and calcification of the epithelial cells especially of the first portions of the proximal convoluted tubules. The degenerated cells, some partially calcified, are cast off into the lumen as fragments or complete cells with granular or vacuolar degeneration. Active epithelial regeneration takes place along with degeneration of adjacent or overlying cells. The epithelial cells show mitotic figures, flattened basophilic cytoplasm with hyperchromatic nuclei, and small polypoid accumulations—all evidence of regenerative activity. The occurrence of calcification is not necessarily dependent on the degree of epithelial degeneration in the sense that instances of marked degeneration are noted without calcification despite an adequate lapse of time (plate 113).

It is assumed that when calcification does occur, it is localized to necrotic cells. However, this is really not an observation but merely an unproved interpretation. Calcification has been

observed in mercurial nephrosis of dogs 24 hours after the mercuric chloride was administered (Hepler and Simonds). The precise chemical reasons for the calcification are not known. Necrosis of cells of the proximal tubules is not sufficient basis, nor are the level of blood calcium, pH, the time of action, or the dosage of the poison the determining factors. The role of phosphatase is not clear although it has been observed experimentally that regenerating tubular cells are resistant to the repeated action of mercuric chloride (as well as of uranium nitrate), and these cells are known to have a diminished content of alkaline phosphatase. Fat (Hepler and Simonds) or protein (Gomori) is thought to play a possible role in the calcification. The calcium has a particular affinity for the nuclei of cells and we have seen calcification even of chromosomes of regenerating epithelial cells in mitosis. This latter observation indicates that regenerating cells in the kidney of the human are not completely resistant to the effects of the poison.

Casts of protein, epithelial, cellular detritus, some inflammatory cells, and blood are found in the distal tubules. Calcified material in this debris is not commonly seen. Moderate dilatation of the lumens of the proximal tubules is frequently present. The interstitial tissue is often edematous and focally infiltrated in scattered areas with plasma cells and lymphocytes. Occasionally a small focus of thrombophlebitis is found resulting from destruction of an adjacent tubule.

As a rule, the glomeruli are histologically negative or show a slight focal increased endothelial cellularity. Rarely, there is an associated acute diffuse proliferative glomerulonephritis. In sharp quantitative contrast are the experimental findings of Hunter and Roberts who report frequent, "degenerative," functionally significant glomerular changes in rabbits and monkeys, poisoned with mercury bichloride, as well as with uranium nitrate. It is possible that actual photomicrographs might have been more convincing than the drawings which they appended. In addition to the glomerular and tubular changes, we have found that the afferent arteriole, even in young normotensive individuals, may be acutely thickened by smudgy

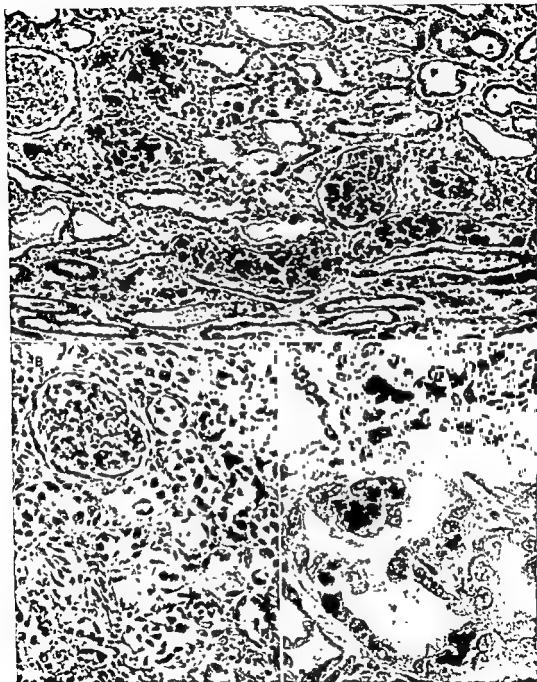


FIG A *Mercury bichloride poisoning (after 10 days) with extensive necrosis, calcification and desquamation of epithelium of proximal convoluted tubules. Interstitial edema and inflammation are also present. The tubules are only slightly dilated and the glomerulus is not remarkable.*

FIG B *Mercury bichloride poisoning with similar clinical history (dosage and duration) as in case illustrated in figure A, showing extensive necrosis of tubular epithelium but without calcification.*

FIG C *Higher magnification of section of figure A showing necrosis, polypoid regeneration and calcification of epithelium of proximal convoluted tubules.*

hyalin resembling somewhat the arteriolar change of malignant nephrosclerosis.

Finally, it is of interest to note that the preponderance of the degenerative change tends to be selectively localized to the peripheral portions of the cortex as opposed to the juxtamedullary regions. This distribution suggests that the location of the damage may in part be determined by circulatory factors.

We have not seen an identical type and location of calcific deposits in association with the degenerative and regenerative histologic picture in human kidneys caused by chemicals other than mercurials. However, similar calcification has been reported in human cases of bismuth poisoning (Weller), and in dogs poisoned with uranyl nitrate and potassium dichromate in 45 per cent and 25 per cent of animals respectively. However, as plates 113, 114, 115 and 116 show, extensive necrosis of tubular epithelium need not lead to calcification in these human cases of poisoning by potassium bichromate or potassium chlorate.

### *Pathologic Physiology*

Experimentally, renal damage by mercuric chloride, as well as by uranium nitrate, may be prevented by ligation of the ureter. This is not true of the changes produced by hypertonic solutions (Wilmer). The presumption is that the ureteral ligation soon stops glomerular filtrate so that the poison does not come in direct contact with tubular epithelium or, at least, is not concentrated there (Wilmer). The oliguria or anuria is usually explained on the basis of Richards' observations on frogs poisoned with mercuric chloride. His direct measurements by pipets introduced into the nephron revealed a normal amount of glomerular filtrate which he assumed was more or less completely returned to the peritubular capillaries across the ineffectual necrotic epithelial barrier. It is not at all certain, however, that the conclusions from these experiments on frogs are applicable to conditions in man.

As in the case of hemoglobinuric nephrosis, recovery is heralded by a rather sudden onset of diuresis, a reaction difficult to explain if the anuria is the result merely of marked tubular epithelial degeneration, regeneration of epithel-

ium is not that spontaneous. The presence of shock early in the course and the sudden diuresis with recovery make it difficult to dismiss the thought that a vascular constrictive element is also at work, probably effecting a reduction in glomerular filtrate. No permanent renal damage follows clinical recovery from the poisoning although the ability to concentrate the urine may be impaired for weeks, just as in cases of hemoglobinuric nephrosis.

The mercury may be detected by chemical examination of the kidney as well as liver, feces, urine and the gastric contents if available early. Mercury may be found in the urine 3 to 24 hours after the poisoning (Lambert and Patterson). In addition to the renal damage, mercuric chloride produces diphtheritic, hemorrhagic necrosis of the mucous membranes contacted, as well as a hemorrhagic colitis that is pathologically like that of severe bacillary dysentery, the colitis of aplastic anemia or uremic colitis. In the case of mercury poisoning, the colitis has been attributed to the excretion of the poison by the large bowel. This presumption has led to the use of a cecostomy to drain the excreted mercury and to prevent further reabsorption.

### POTASSIUM DICHROMATE NEPHROSIS

The principal lesion of potassium dichromate ( $K_2Cr_2O_7$ ) nephrosis is a marked necrosis of the tubular epithelium of the proximal portion of the nephron extending down to the loop of Henle. As with some other advanced necrotizing nephroses involving this portion of the nephron, such as those due to mercury bichloride and potassium chlorate, the damaged epithelial cells are more brightly eosinophilic than normal and the cytoplasm is converted into a mass of acidophilic hyaline granules. As Opie has shown, the osmotic pressure of such cells is considerably reduced, and, on this basis, the hyaline granules may be formed. The cellular detritus often fills the lumens of the proximal tubules, and, because of its coalescence, may resemble amorphous protein precipitate. Usually the desquamated masses in the lumens are surrounded by regenerating tubular epithelium. Cast off cells in mitosis may be observed in the midst of the luminal debris. The



FIGS. A AND B *Potassium dichromate nephrosis* showing varying stages of degeneration, regeneration and desquamation of epithelium of proximal convoluted tubules. The hyperchromatic cells are in the stage of regeneration.


nuclei of the desquamated cells quickly become pyknotic, distorted, and finally disappear so that large casts of anuclear cytoplasm of sloughed cells, occasionally intermixed with leukocytes, occupy the lumens of the proximal tubules. Focal, slight to moderate dilatation of these tubules is apparent. Some of the cellular debris reaches the collecting tubules, but not enough to cause significant obstructive change.

The interstitium is moderately edematous and there is a mild interstitial inflammation. The glomeruli are not remarkable. Some of the afferent arterioles, as in the mercury kid-

### GLYCOL NEPHROSIS

The toxic glycols and their formulas are listed in table 7. These compounds are used as detergents and preservatives and are employed in antifreeze agents, in the manufacture of lacquers, cosmetics, flavoring extracts and textiles. Diethylene glycol, the carbitols, dioxane and dipropylene glycol all have an ether linkage between the molecules of glycol and they all produce similar renal lesions in contrast to those caused by ethylene glycol, ethylene glycol diacetate and propylene glycol, which lack the ether linkage.

TABLE 7.—The Toxic Glycols and Their Formulas

Ethylene glycol (antifreeze)	$\text{HO CH}_2\text{CH}_2 \text{OH}$
Ethylene glycol diacetate	$\text{CH}_3\text{CO O CH}_2\text{CH}_2 \text{O CO CH}_3$
Propylene glycol	$\text{HO CH}_2 \text{CH OH CH}_3$
Diethylene glycol (diglycol)	$\text{HO CH}_2 \text{CH}_2 \text{O CH}_2 \text{CH}_2 \text{OH}$
Ethyl diethylene glycol (carbitol)	$\text{C}_2\text{H}_5 \text{O CH}_2\text{CH}_2 \text{O CH}_2 \text{CH}_2 \text{OH}$
Methyl diethylene glycol (methyl carbitol)	$\text{CH}_3 \text{O CH}_2 \text{CH}_2 \text{O CH}_2 \text{CH}_2 \text{OH}$
Butyl diethylene glycol (butyl carbitol)	$\text{C}_4\text{H}_9 \text{O CH}_2 \text{CH}_2 \text{O CH}_2 \text{CH}_2 \text{OH}$
Diethylene dioxide (dioxane)	
Dipropylene glycol	$\text{CH}_3 \text{OH CH}_2\text{CH}_2 \text{O CH}_2 \text{CH}_2 \text{OH CH}_3$

neys, show acute, acellular, diffuse, hyaline, acidophilic alteration (plate 114).

### POTASSIUM CHLORATE

Potassium chlorate ( $\text{KClO}_3$ ) is used industrially in the manufacture of explosives and in medicine as a component of mouth washes. Poisonings occur from accidental, suicidal or homicidal ingestion. The symptoms are those produced by ingested corrosive poisons and include immediate vomiting, diarrhea, abdominal pain, dyspnea, cyanosis, convulsions, coma and death. Methemoglobin is formed and the urine may be colored dark by its excretion.

The renal histologic reaction (plate 115) is not that of hemoglobinuric nephrosis but of a proximal nephron nephrosis of a quality very much like that due to potassium dichromate, described previously, and to potassium bromate (neutralizer of "cold wave" lotion).

### Ethylene Glycol Nephrosis

Ethylene glycol (antifreeze— $\text{HO CH}_2 \text{CH}_2 \text{OH}$ ) has been injudiciously drunk for its intoxicating effects, or consumed mistakenly, as in the cases in which it was inadvertently used in the preparation of coffee. A number of fatalities have been reported. The lethal dose is estimated at 100 cc., but survival has followed the consumption of 240 cc. Ethylene glycol is a colorless, odorless fluid, with a not unpleasant, bitter-sweet flavor. It is about twice as toxic as propylene glycol and half as toxic as diethylene glycol.

### Clinical picture

The early signs and symptoms of poisoning include severe vomiting, excitation simulating alcoholic intoxication, convulsions, severe pulmonary edema, prostration and shock. If this initial stage, lasting up to about 24 hours is



FIG. A *Potassium chlorate nephrosis* showing necrosis of epithelium of proximal tubules. The glomeruli are spared.

FIG. B *Potassium chlorate nephrosis* with extensive necrosis of tubular epithelium and obliteration of lumens of tubules by epithelial debris in association with focal interstitial edema and inflammation.

survived, the patient develops signs and symptoms of renal insufficiency with death as the usual but not inevitable outcome. One case recovered completely despite the fact that the nonprotein nitrogen level of the blood reached 158 mg. per cent one week after the poisoning. Anuria may or may not be present in the initial stage but subsequently develops along with uremia.

### *Pathology*

The significant findings at autopsy are limited to the lungs, brain and kidneys. The lungs show marked congestion and bronchopneumonia. The brain is either grossly normal or edematous with flattened convolutions and occasional petechiae. Histologically, there is leptomeningeal perivascular infiltration with neutrophilic leukocytes, lymphocytes and histiocytes and minimal changes in ganglion cells. Small refractile crystals may be demonstrable in the walls and lumens of the vessels, in the parenchyma and in the meninges. Often the crystals are not associated with inflammation in their vicinity.

The kidneys are swollen but not otherwise remarkable. The chief histologic features are (1) birefringent crystals of calcium oxalate in the lumens of proximal convoluted tubules and (2) diffuse dilatation of this portion of the nephrons. The crystals are large, light yellow, and arranged as sheaves, prisms or rhomboids. They frequently extend across the entire lumen of the dilated tubule which also contains granular protein precipitate (plates 117, 118). The epithelium of the proximal tubules may be somewhat flattened because of the dilatation but shows no significant degenerative or regenerative changes, despite apparent puncture by the needle-like crystals. The glomeruli are not remarkable except for dilatation of Bowman's spaces. Mild focal interstitial mononuclear inflammation and edema are usually present.

This is essentially the lesion produced experimentally by ethylene glycol or by the dactate. As would be expected, it is also the picture that follows the accidental ingestion of the corrosive poison, oxalic acid ( $H_2C_2O_4 \cdot 2H_2O$ ), if the patient survives the initial stage of col-

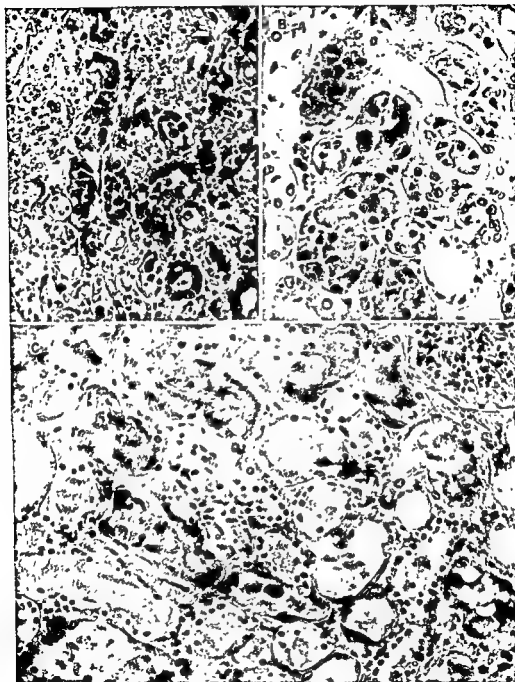
lapse. Propylene glycol, of the same group of compounds, produces, after intravenous injection, hemolysis, azotemia and a histologic picture of heme casts in the kidney resembling hemoglobinuric nephrosis (Kesten et al.).

Most observers have ascribed death in ethylene glycol poisoning to pulmonary edema and acute cardiac failure or to renal failure (Milles). Others (Pons and Custer) have attributed death primarily to lesions of the central nervous system and in only one of their 18 cases was "renal damage severe enough to contribute to a fatal outcome. . . in the other cases there was nothing beyond simple deposition of calcium oxalate." However, their conclusion is not supported by data on urinary output, specific gravity, or renal function tests, except for three determinations of urea nitrogen in two patients.

Evaluation of the role of the kidney in this poisoning can hardly be dismissed on such limited data. The cerebral component may perhaps be a significant one in connection with shock and pulmonary edema, but the possibility of serious renal dysfunction ought not to be gainsaid in the presence of great numbers of partially obstructing crystals, with tubules showing varying degrees of internal hydropnephrosis (plate 118 B), even if concomitant inflammatory or degenerative changes are absent. It is true that much more data are needed for final evaluation, including information on potassium levels, and on other possible end-products of the glycols, inasmuch as only about 10 per cent of the ethylene glycol is accounted for by the calcium oxalate. As the situation stands, renal insufficiency appears to be the usual mode of death in those individuals who survive the first few days and expire several days later.

### *Diethylene Glycol*

The general awareness of the toxicity of diethylene glycol was dramatically precipitated in 1937 by the occurrence of 76 deaths from the ingestion of 2 to 4½ ounces of an elixir of sulfanilamide. The elixir contained 72 per cent diethylene glycol. The symptoms started 3 to 5 days after ingestion of the elixir and included nausea and vomiting, heartburn, abdominal cramps, diarrhea, facial edema, slight icterus,



FIGS A AND B *Atabrine nephrosis*. The epithelium of the proximal nephron is in the various stages of degeneration. The shrunken nuclei of some of these cells simulate those of plasma cells. The atabrine had been used daily for months. Atabrine nephrosis is a rare complication.

FIG C *Necrosis with regeneration of cells of proximal nephrons in acute proliferative glomerulonephritis*. This marked tubular reaction may be confused with a primary chemical necrotizing nephrosis, when, in reality, the tubular changes are secondary to the glomerular ischemia. The hyperchromatic cells are the regenerating ones. (A F I P. Acc 101695)



back pain, oliguria, anuria and uremia. Serous effusions were present in some of the patients. No hypertension or anemia was noted. Death occurred in 18 to 21 days. There was considerable variation in response to the drug inasmuch as more than 100 persons took the toxic elixir without clinical effect.

#### *Pathology: liver*

The principal pathologic findings were in the liver and kidneys. The livers were not grossly altered except for moderate enlargement. The histologic picture of the liver is striking and is apparently specific for the group of glycols with the ether linkage. The hepatic cells of about one third of the central portion of all lobules are uniquely altered. The alteration involves the collar of cells immediately about the central vein. The involved zone is sharply demarcated from the outer two thirds of the normal peripheral parenchyma (plate 119 B). The granular acidophilic cytoplasm of the normal cell has been replaced in the involved zone by cells swollen by fluid in fine or coarse droplets that do not take the stain for fat or glycogen. The nuclei are pyknotic. Remarkably enough, no noteworthy congestion or inflammatory reaction accompanies this parenchymal change in any part of the lobules.

#### *Pathology kidneys*

The damage to the kidneys is even more striking. In eight of twelve cases (Geiling and Cannon) bilateral cortical necrosis was present. In all cases, however, there is a destructive coarse vacuolization of the cells of the proximal tubules. The histologic stages in this degenerative process range from hyaline droplet swelling of the granules of the epithelial cells to complete disruption of the cell walls and extrusion of part or all of their contents (plates 119 A, 120 B). Cells are frequently seen in which the hyaline granules are in the process of being cast off from the cell into the tubular lumen. The vacuolization itself is of an order similar to that of the liver. It is generally coarse resembling the glycogen vacuolization of diabetes mellitus, or of that associated with choleraic nephrosis or ulcerative colitis (plate 108 B), rather than the finely multiloculated vacu-

olar changes produced by fat or following the administration of hypertonic sucrose solution (plate 106). There is no mistaking the irreversibly destructive nature of the vacuolization wrought by diethylene glycol in contrast to the blander lipid, sucrose or glycogenic vacuolization. Diethylene and related glycols are markedly hygroscopic and this property may form the basis for what is tantamount to the destruction of the tubular cells by the suctioning of their contents into the tubular lumens.

The nuclei of the epithelium of the proximal convoluted tubules, again resembling those of the liver cells, are pyknotic, distorted and displaced to a corner of the cell, or altogether extruded into the lumen.

The glomeruli, except as they are involved in the cortical necrosis, show no significant change.

In the distal convoluted tubules, the only change of significance is the presence of isolated, deeply basophilic, spherical crystals with radiating lines. The crystals are birefringent and are more or less the size of an epithelial cell of these tubules. They are quite like those we have found associated with a great variety of acute viral and known chemical degenerations of the liver. They resemble leucine but their precise nature is unproved.

#### BISMUTH INCLUSIONS

A rather unique variety of intranuclear and intracytoplasmic inclusion is found in the kidneys of patients who have received bismuth from such sources as bismocyanol (bismuth derivative of camphocarbonic acid) and bismuth tartrate. Similar renal inclusions have been observed in rats injected intramuscularly with bismocyanol and sodium potassium tartrate (Pappenheimer and Maechling). The in-

the nuclei and cytoplasm of the proximal convoluted tubules and are easily recognized with routine stains (plate 121). They are not necessarily associated with histologic evidence of cellular damage. In a convincing set of photomicrographs, Pappenheimer and Maechling demonstrate the extrusion of these bodies from

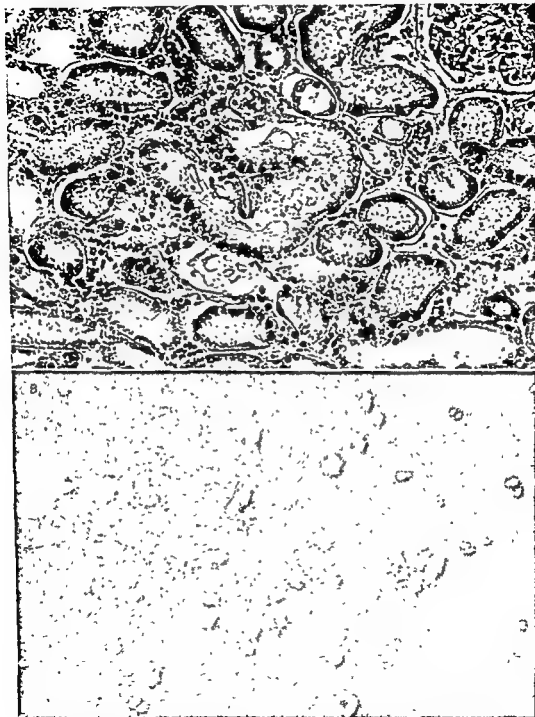


FIG A *Ethylene glycol (antifreeze) nephrosis* Crystals of calcium oxalate arranged in sheaves and protein precipitate are seen in lumens of proximal convoluted tubules

FIG B Crystals of calcium oxalate in proximal convoluted tubules are shown in photograph taken with incompletely rotated polarized light so as to indicate their position in the nephron. If the initial cardiac failure, pulmonary edema and shock are survived, death is due usually to renal failure. Encephalitis is said to account for some deaths

the nucleus to the cytoplasm of the tubular epithelial cell.

That these inclusions actually are bismuth compounds has not been proved. The inclusions are easily distinguished from proved (e.g., encephalitic) epithelial viral inclusions (plate 121), and from the lesions of so-called "inclusion" disease (plate 122). The nuclear inclusions following lead poisoning (Blackman) are similar to those due to viruses.

In addition to the specific inclusion bodies, calcification following necrosis of renal tubular epithelium has been reported after the injection of bismuth compounds in both humans and experimental animals (Weller). However, no calcification was noted by Pappenheimer and Maechling in the kidneys of either humans or animals treated with various bismuth preparations.

#### INCLUSION DISEASE OF INFANTS

In 1904, there were described, apparently for the first time, peculiar inclusion bodies in the tubular epithelium of infants (Jesonek and Kiolemenoglou, Ribbert). These inclusions were then regarded as protozoan, an impression that received more definitive confirmation from Smith and Weidman who identified the inclusions as a form of ameba which they termed *Entamoeba mortinatalium*. These inclusions were soon found in other organs, especially the parathyroid, pituitary and salivary glands; less often in the kidneys, bile ducts, liver, pancreas, lungs, rarely in the thyroid, epididymis, intestine and brain. Their similarity to those cutaneous inclusions of varicella described by Tyzsa in 1906 was first indicated by Goodpasture and Talbot in 1921. In the same year Lapschutz concluded that the intranuclear inclusions of herpes really represented specific reactions to a specific virus. This impression was extended to a generalization that nuclear Type A inclusions, similar to those under discussion, indicated a localization of the infective viral substances [Goodpasture (1929)]. Because the virus has never been isolated or transmitted to animals, the proof of the viral nature remains inferential and incomplete.

This hiatus in the evidence does not justify the skepticism accorded the viral concept of

the lesions (Pinkerton). Morphologically similar inclusions in renal epithelium are said to be produced with lead and bismuth poisoning, and by certain aluminum and ferric compounds (Olitsky and Harford). However, the renal epithelial inclusions attributed to lead poisoning are stated to be acid-fast, in contrast to the viral inclusions (Wachstein). The latter are actually mildly acid-fast. Moreover, we find that the large, haloid, highly characteristic, inclusion bodies of "inclusion disease," within the epithelium of the distal convoluted tubules, are easily distinguished from the lead or bismuth lesions even in sections stained routinely with simple hematoxylin-eosin (plates 121, 122). Fat is present in the perinuclear, clear zone.

Inclusion disease of infants has not been diagnosed clinically. It occurs in the salivary glands of infants, mostly under one year of age, in about 12 per cent of routine autopsies of this age group, inclusions in the kidneys are found in about 1 per cent of autopsies of infants. Indistinguishable inclusion bodies are found in the salivary glands of guinea pigs (Pearson).

Involvement of the kidney gives rise to no signs or symptoms, but, as Pinkerton points out, the possibility exists that the cells with the inclusion bodies could be found by examination of the urinary sediment. This "inclusion disease" may be responsible for the death of infants, particularly on the basis of pulmonary and hepatic involvement (Vellios and Smith).

Farlane: J. Path. & Bact. 59: 395-398, 1947)

#### PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (MARCHIAFAVA-MICHELÌ SYNDROME)

Credit is given to Marchiafava (1911) and to Michelì (1931) for clarifying as a separate entity the disease now known as the Marchiafava-Michelì syndrome, paroxysmal nocturnal hemoglobinuria, or chronic hemolytic anemia with nocturnal hemoglobinuria.

#### Clinical Picture

The disease occurs in previously well individuals mostly between the ages of 20 and 40 years, equally divided between the sexes, rather

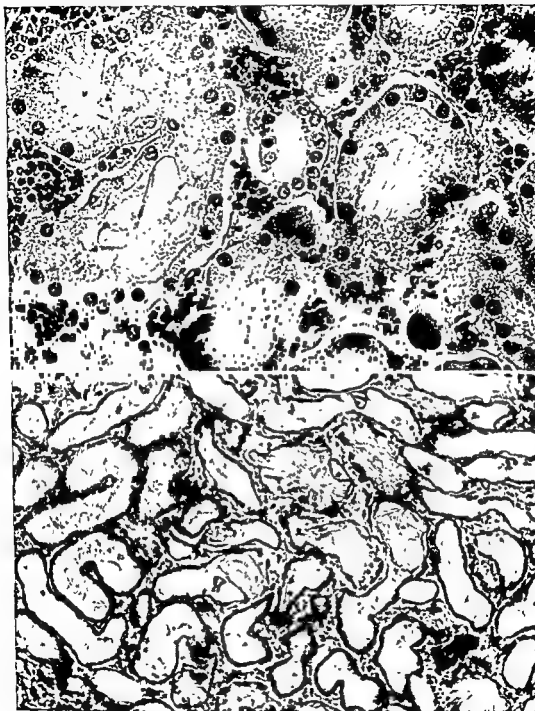


FIG. A Ethylene glycol (antifreeze) nephrosis with crystals of calcium oxalate in proximal convoluted tubules, the brush borders of which are clearly identifiable. This patient consumed 200 cc of the poison. (A F I P 116300)

FIG. B Ethylene glycol nephrosis with dilatation of tubules (internal hydronephrosis) due to blockage by the crystals of calcium oxalate shown herein

than preponderant among males as formerly thought (Manchester) The youngest patient reported was 5 years old (Manchester)

The clinical picture is characterized by acute attacks of hemolysis and hemoglobinuria, coming on during sleep. It does not matter if the hours of sleep take place during the day or night Episodes of hemolysis may be provoked by infections, even mild upper respiratory tract infections, by the menses, by the administration of acid salts, or by abruptly curtailing alkali therapy. Exposure to sun, prolonged chilling, exercise, food, or a positive syphilitic serology (as in paroxysmal cold hemoglobinuria) have no bearing on the disease.

The clinical symptoms are those of anemia. Immediately after the attack, there may be headache, backache, and abdominal and muscular cramps Thrombosis of veins has been observed in about 25 per cent of cases (Ross).

Fatalities occur in most cases, in from 5 to 15 years, from thrombosis of large visceral veins, intercurrent infections, anemia, and operative mortality (Manchester) Hemoglobinuric nephrosis is not a part of the picture unless it follows an incompatible blood transfusion. Splenectomy and even transfusions are of little help as supportive measures and there is the added risk of the hemolytic reactions in the latter instance.

### Diagnosis

The clinical diagnosis of paroxysmal nocturnal hemoglobinuria is confirmed by the demonstration of hemolysis of the patient's cells in the patient's or in normal serum acidified to pH 6.8 to 7.0. The hemolytic factor may be destroyed by heating the serum to 56° C. for 20 to 30 minutes There is no increased fragility to hypotonic saline, no spherocytosis, and the Donath-Landsteiner phenomenon does not occur. The defect is therefore in the patient's red blood cells rather than in the serum

There is no unequivocal proof that the pH or carbon dioxide combining power of the blood becomes lowered during sleep, although some data are available (Hastings and Eisele) The *in vivo* counterpart of the phenomenon of hemolysis with acidified serum in the test tube is the unexplained Oxyhemoglobinuria, meth-

emoglobinuria, and, in protracted cases, the diagnostically important feature of hemosiderinuria may be noted

### Pathology

The kidneys, which are usually the site of deposition of hemosiderin after a period of years of this disease, are moderately enlarged and brown with hemosiderin (plate 123 A) Even grossly, it is seen that the hemosiderin is confined to the cortex including the columns of Bertin (plate 123).

Histologically, the hemosiderin is practically confined to the epithelium of the proximal convoluted tubules, unlike the distal localization of hemosiderin in hemochromatosis (plate 124) The pigment is fairly easily recognized in the routine sections by the refractile, hard-appearing, relatively irregular, sharply bordered granules The stains for iron (e.g., Perl's stain) are strongly positive. However, with experience they can most often be distinguished in routine stains from granules of melanin, or from lipochromes that may be present in the tubular epithelium.

It has been generally assumed that the hemosiderin granules are engulfed in the process of athrocytosis by the proximal epithelial cells from the fluid in the tubular lumen The possibility that the hemosiderin is dissociated from the globin directly within the epithelium, and that the granules of hemosiderin are formed intracellularly, seems to have been discounted without good reason Actually, the hemoglobin released in the plasma in hemolytic episodes is in solution, and is not particulate It appears to pass the glomerular filter, and to present itself to the cells of the upper part of the proximal nephron in solution Lower in the nephron, with changes in pH and electrolytes, the hemoglobin may become particulate In principle, a similar type of reasoning applies to the presumed athrocytosis of "droplets" of protein from the lumens of the proximal tubules (page 216)

Heme casts, necrosis of tubular epithelium, or focal interstitial nephritis are not present, so that there is no histologic basis for confusion of this lesion with that of hemoglobinuric nephrosis Some hemosiderin may be present also in

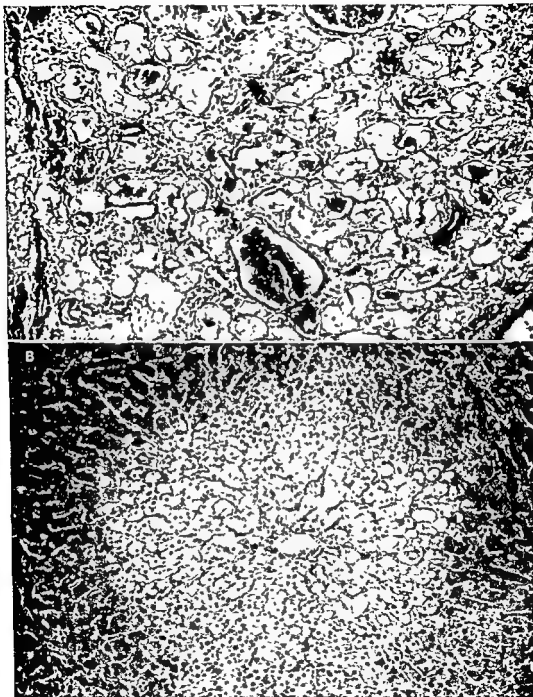


FIG. A *Diethylene glycol nephrosis*. The severely destructive hydropic degeneration of tubular epithelium, principally of the proximal nephron, is shown.

FIG. B *Hydropic degeneration of hepatic cells about central vein* is characteristic of toxicity due to diethylene glycol and other related glycols. As indicated these vacuoles do not show evidence of glycogen or fat and this type of pericentral degeneration involves all hepatic lobules.

the glomerular epithelium and in the interstitial macrophages. As mentioned, thrombosis of the veins of the kidney (and other organs) may occur.

### Pathologic Physiology

It is of considerable interest that the renal threshold for the excretion of hemoglobin (normally about 100 mg. per cent in plasma) may be progressively depressed to as low as 46 per cent of normal. In other words, normally, the plasma hemoglobin (molecular weight 68,000) that passes the glomerular filter is promptly reabsorbed across the epithelium of the proximal convoluted tubules. When the tubular cells become loaded with hemosiderin, however, the reabsorption is hindered, as if the intracellular granules of hemosiderin were a mechanical barrier to the transfer of additional hemoglobin or its products. Under this circumstance, therefore, hemoglobinuria occurs at low plasma levels of hemoglobin. This barrier, remarkably enough, does not affect other substances, such as glucose, that are normally absorbed across this segment of the nephron. If the interval between the hemolytic crises is prolonged, the opportunity is afforded for the tubular epithelial cells to rid themselves of the hemosiderin by its excretion in the urine as hemosiderinuria, or by its return to the blood. At the same time, the renal threshold for hemoglobin correspondingly and gradually rises. Actually this principle of saturation is the basis for studies of maximal clearance (i.e.,  $T_m$ 's).

The presence of hemosiderin in the epithelium of the proximal convoluted tubules is not a qualitatively specific lesion. Hemosiderin occurs in this location in other hemolytic anemias, and as a result of multiple transfusions. It is remarkable, however, to note that in these latter conditions, there is, as a rule, a wide disparity between a small amount of renal hemosiderosis in contrast with the hemosiderosis of

the liver, spleen and lymph nodes. Quite the reverse is true of the organs in paroxysmal nocturnal hemoglobinuria, so that this diagnosis may safely be suggested when conspicuous hemosiderosis is practically confined to the kidney (plate 124). For reasons that are altogether obscure, the renal hemosiderin in hemochromatosis, and in unusual instances of hemolytic anemias associated with marrow mast cells, selects the distal convoluted tubules (plate 124 C).

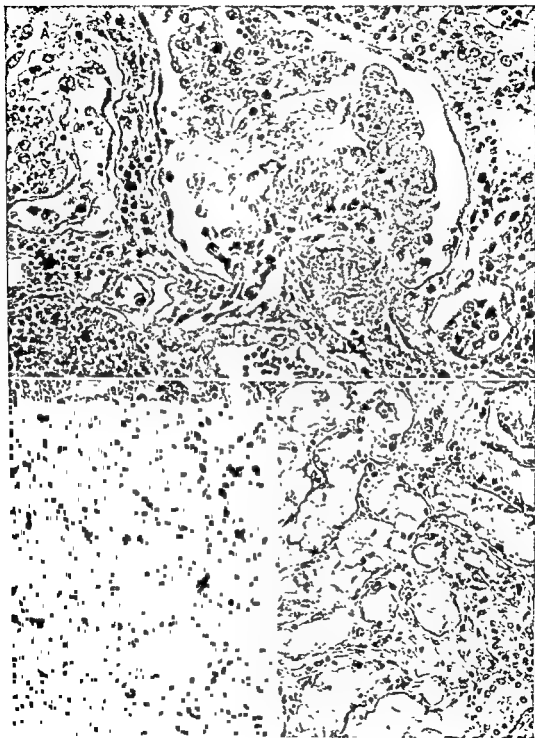
### FAVISM

Favism is another form of paroxysmal hemoglobinuria that has been rather loosely incorporated into the category of conditions that commonly cause hemoglobinuric nephrosis with death from renal insufficiency. This point of view deserves to be re-examined to see if it is justified by available documentation. Besides, "natural" experiments in patients with hemoglobinemia are of particular importance in throwing light on the pathogenesis of hemoglobinuric nephrosis. It is clear from the hemolysis that occurs in hemolytic diseases, such as congenital or acquired hemolytic icterus, and from paroxysmal nocturnal and cold hemoglobinurias, that hemolysis alone does not produce the dramatic picture of hemoglobinuric nephrosis with renal insufficiency. In favism, at least two additional, perhaps critically pertinent, factors often operate in addition to the hemolysis: (1) allergy and (2) shock.

Favism has in most cases a familial background of the disease; it occurs in Sardinia, Sicily, and southern Italy. Rare cases have been reported in Palestine (Robinson), and even in the United States (McCrae and Ullery; Josephs). It results from inhalation of the blossom pollen dust or from the ingestion of the bean of the plant, *Vicia faba*, related to the lima bean family. This plant is cultivated extensively in some of the states, especially New

FIG. A *Diethylene glycol nephrosis* showing thrombosis of glomerular capillaries and afferent arteriole as part of the associated bilateral cortical necrosis

FIG. B *Diethylene glycol nephrosis* is commonly combined with bilateral cortical necrosis as here indicated. The necrosis is shown at the left and the characteristic tubular vacuolization is at the right. The vacuolization simulates that seen in ulcerative colitis or dysentery (plate 108, figure B) but it is far more destructive



(Legends on facing page )



Jersey, New York, Illinois and California (Luisada). The reason so few cases of favism occur in this country is, therefore, not clear.

The disease is characterized by an acute onset of nausea, vomiting, fever, abdominal pain, pallor, icterus, vertigo, hemoglobinuria, and, in severe cases, rapid collapse and death in two to three days. The attack is said not to occur with the first contact with the bean nor in those who eat the bean regularly throughout the year. The onset of symptoms may take place within a few minutes after inhalation of the pollen, or may be delayed one to three days. In those countries in which favism is likely to occur, the diagnosis of blackwater fever enters the differential picture. Death in about 8 per cent of cases (McCrae and Ullery) occurs from overwhelming hemolysis and shock, especially in children. Rarely, death has been attributed to hemoglobinuric nephrosis but the evidence is incomplete. So very few necropsies of these patients have been recorded, and so sparse has been the documentation of the clinical cases from the renal point of view, that a definitive statement is not warranted on the data available. However it appears that the syndrome of hemoglobinuric nephrosis, if it occurs at all in favism, is uncommon and is related not only to the overwhelming hemolysis which may destroy one of every five red blood cells, but to the associated shock and possibly also to the allergy. In this connection, it is pertinent to note the case of hemoglobinuria caused by the venom from multiple bee stings in which there was rapid recovery with no evidence of hemoglobinuric nephrosis (Kosalka).

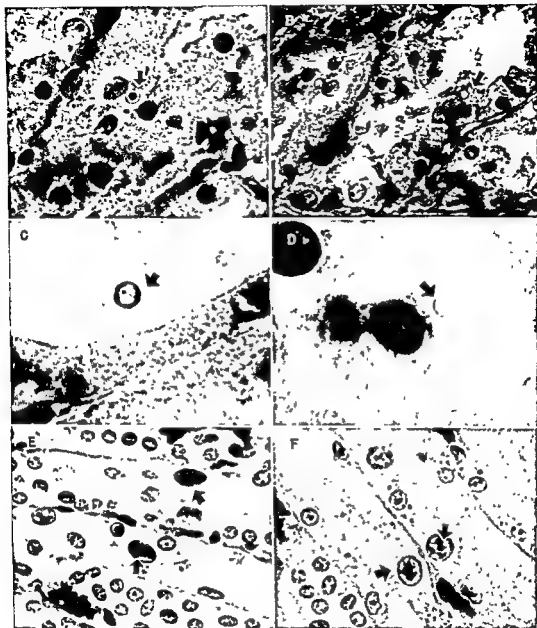
#### MARCH HEMOGLOBINURIA

A form of hemoglobinuria and hemoglobinemia, first described in 1881, occurs infrequently among previously healthy young men, after exercise such as walking, marching or running. It is a remarkable fact that in these same individuals exercise not taken in the upright position, such as cycling or swimming, does not precipitate an attack (Gilligan and Blumgart). With minor exceptions, for example backache, the only symptom of the disease is the observation by the patient of "blood" (hemoglobin) in his urine, anemia and icterus occur

rarely. The hemoglobinuria is associated with hemoglobinemia which may reach levels as high as 220 to 230 mg per cent. No urinary suppression occurs in the uncomplicated disease, that is, hemoglobinuric nephrosis is clearly not a part of the picture. The course of the disease is benign and self-limited; the attacks cease spontaneously after a few months to a few years. The episodes of hemoglobinuria may be induced at will with exercise, but there is no significant association with acidosis, syphilis, cold agglutinins, detectable fragility of red blood cells, sleep, malaria, infection, lordosis, or the ingestion of fava beans. There is no evidence of any form of desensitization as a result of repeated attacks. Striking results have been achieved therapeutically by the administration of ascorbic acid (Lubran and Sakula).

#### Pathogenesis

The cause of the hemolysis is unknown. The requirement of exercise in the upright position has led to the suggestion that the mechanism may be related to that concerned with orthostatic albuminuria. However, lordosis which is usually present in cases of orthostatic albuminuria is uncommon in persons with march hemoglobinuria, according to Lubran and Sakula. Moreover, as these authors mention, march hemoglobinuria involves both kidneys whereas only the left kidney is said to excrete the protein in orthostatic albuminuria (Hinman). Finally, orthostatic albuminuria is not associated with march hemoglobinuria. It is known that a mild degree of hemoglobinemia of the order of 14 mg per cent occurs normally after severe exercise (Gilligan et al.). It appears established that the renal threshold for the excretion of hemoglobin is considerably lowered in instances of march hemoglobinuria from the normal of about 100 mg. per cent to about 30 mg. per cent. This fact alone does not explain the problem inasmuch as levels over 200 mg per cent are reached in this disease. The predisposition of some individuals to develop an exaggerated hemolysis during exercise is explained by Lubran and Sakula on the basis of the discharge into the general circulation of a small percentage of fragile red blood cells by the excessively contracting spleen. However, spon-



FIGS A, B, C AND D *Bismuth inclusions* (arrows) are in the epithelium or lumen of the proximal convoluted tubules. They are not doubly refractile.

FIGS E AND F *Acidophilic viral inclusions* in the limbs of Henle from a case of St. Louis encephalitis (arrows).

taneous cures and the response to ascorbic acid are difficult to reconcile with this theory.

### PAROXYSMAL COLD HEMOGLOBINURIA

Paroxysmal cold hemoglobinuria occurs almost exclusively in syphilitic individuals, principally congenital syphilitics, in only about 5 per cent of cases is there no clinical or serological evidence of syphilis. The attack of hemoglobinemia and hemoglobinuria (oxyhemoglobinuria and methemoglobinuria) takes place in from a few minutes to seven or eight hours after the exposure to cold. The exposure may be remarkably slight, cold drinks may start an attack. Rarely, as in cases of *virus pneumonia*, hemoglobinuria occurs as a result of the production of cold agglutinins in the absence of syphilis.

The attack is very much like those of other forms of paroxysmal hemoglobinuria and consists of aching pains in the back and legs, abdominal cramps, usually chills and fever, and the passage of chocolate colored urine. The specific diagnosis is established by the demonstration of an autohemolysis by the test known as the Donath-Landsteiner phenomenon. This test is performed with a 5 per cent suspension in saline of normal red blood cells, belonging to the same blood group as the patient's blood, to which are added equal parts of the patient's serum and fresh guinea-pig complement. The mixture is chilled for 10 to 30 minutes and is then warmed to 37°C for 30 minutes. If the lysis is present, the blood is hemolyzed. The analogous *in vivo* reaction is known as the Rosenbach test in which hemolysis is induced by chilling the patient's hands or feet in ice cold water for 10 minutes.

Hemoglobinuric nephrosis occurs with extreme rarity in association with this disease. One case was recently reported by Sussman and Kayden but the complication was non-specific. Antiluetic therapy usually reduces the titer of the autohemolysin, and thereby eliminates the attacks.

In summary, paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome), paroxysmal cold hemoglobinuria, favism, and march hemoglobinuria represent diseases that are prognostically either quite benign or, when

lethal, do not cause death by hemoglobinuric nephrosis except possibly in the rarest instances when the setting for such a complication is coincidentally just right. The proper setting may imply particularly shock, allergy, hepatic or prior renal damage.

### HEMOGLOBINURIC NEPHROSIS

#### Introduction

Perhaps no disease of the kidney has given so many observers the impulse to record their impressions in the last decade as has the entity known as *hemoglobinuric or lower nephron nephrosis*. (For reasons to be elaborated in this section, the original term "hemoglobinuric nephrosis" appears to us preferable to "lower nephron nephrosis.") The vast number of cases is accounted for not merely by World War II in which, for example, 10 per cent of autopsied

military and civilian practice. These include the use of sulfonamides, and the availability and free use of blood for transfusions, with the increased opportunity for reactions resulting from a variety of incompatibilities. However, although the literature on the subject has, in these recent years, become voluminous, we seem not to have been brought appreciably closer to a solid understanding of these dramatically oliguric or anuric kidneys than we were a decade ago. And perhaps during this time, we have lost a little of our hold on the pathology of the kidneys in this condition.

#### Etiology

Hemoglobinuric (lower nephron) nephrosis may occur in a wide variety of conditions. These include incompatible blood transfusions, crush injuries, shock, reaction to sulfonamides, rapid hemolysis by the use of distilled water during operative procedures such as transurethral prostatectomy, uteroplacental hemorrhage, high altitude anoxia, heat stroke, blackwater fever (*P. falciparum*), mushroom poisoning, and burns; it may occur, too, in association with acute yellow atrophy, particularly that produced by known chemicals (for example, carbon tetrachloride, chloroform,

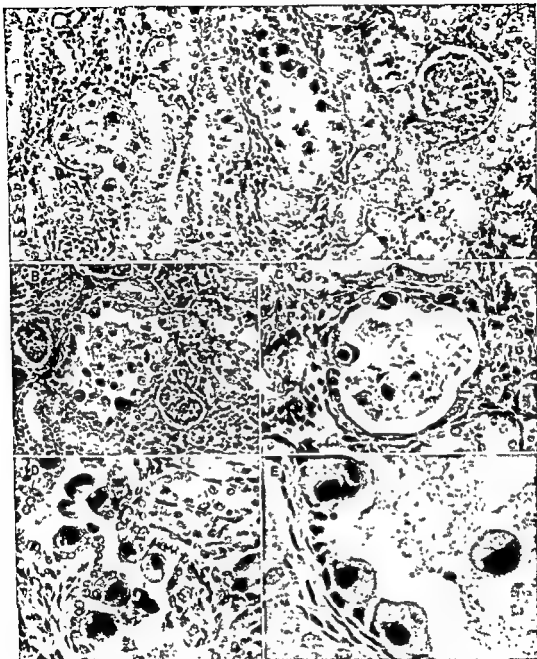


FIG A *Infantile inclusion disease* characterized by enlarged epithelial cells of distal convoluted tubules with acidophilic nuclear inclusions. These are usually incidental findings at autopsy, but infrequently are responsible for death.

FIGS B AND C *Epithelial inclusions* in lining of distal tubule with epithelial debris in lumen. Inflammatory reaction is absent.

FIG D *Epithelial inclusion in distal tubule* identified by intervening uninvolved epithelium. This distal nephron nephrosis is placed in this section for convenience of comparison with other epithelial inclusions.

avertin, and arsenic) Often included in the list of causes of hemoglobinuric nephrosis are alkalosis, and the effects of hemolytic agents, such as photodeveloper (hydroquinone and pyrogallol acid), and the paroxysmal hemoglobinurias (page 241). The clinical and histologic picture of the latter three conditions warrants their distinction not only from each other but also from hemoglobinuric nephrosis

The case of alkalosis cited as an illustration of lower nephron nephrosis was reported originally by McLetchie and deserves some re-evaluation. Alkalosis was present, to be sure, but the patient, who had been vomiting excessively, was also in extreme dehydration and circulatory collapse. Death occurred during an operative procedure. Degenerative and calcific changes were found in the distal nephron but no heme casts were present. Obviously, in the presence of severe dehydration, circulatory collapse, and probably chloride deficiency, mere alkalosis cannot be considered the basic cause of this clinical or histologic picture. The clinical setting has been more or less as complicated in other case reports of "toxic nephritis" (Brown et al.) in which hemoglobinuric nephrosis has been attributed to alkalosis. Moreover, Addis and his associates failed to produce renal damage in rats kept on high sodium bicarbonate intake for 300 days. Renal damage is stated to be produced by chloride deficiency itself (Cuthbertson and Greenberg), but others (Kirsner and Knowlton) fail to confirm this conclusion. The latter also find that severe alkalosis does not produce functional or histologic renal damage. They discount any significant functional effect of the alkalotic parenchymal nephrocacinosis. It is therefore suggested that alkalosis be omitted from the list of causes of hemoglobinuric nephrosis.

The hemolysis and poisoning caused by photodeveloper result in shock, pulmonary edema and rapid death. The renal histologic picture is easily distinguished from hemoglobinuric nephrosis (plate 131 A), by virtue of the thin, almost serous hemolyzed blood, rather than dense heme casts, present in the entire length of the nephron from Bowman's spaces to the collecting tubules. The characteristic feature of paroxysmal nocturnal hemoglobinurias

(Marchiafava-Micheli syndrome) is the abundant collection of hemosiderin in the epithelium of the proximal convoluted tubules (plate 124 A, B), rather than hemoglobinuric nephrosis. This same feature is qualitatively true, although to a lesser degree, of other forms of paroxysmal hemoglobinurias.

### *Clinical Manifestations*

The sequence of clinical signs and symptoms of hemoglobinuric (lower nephron) nephrosis naturally differs somewhat with the etiologic circumstances. Several of these will be considered.

### *Incompatible transfusions*

The reaction following the administration of incompatible transfusion depends on the titer of the isoantibody, on the amount of incompatible blood administered, on associated diseases, and on whether or not the patient is anesthetized. Ordinarily, the patient responds immediately to the incompatible blood with chills, fever, backache, nausea and vomiting and occasionally urticaria. The response to an incompatible transfusion may be completely obscured while the patient is under anesthesia. Often the first indication of the incompatibility is the remarkably severe hemorrhagic tendency such patients develop, so that the enigmatic capillary oozing of blood from the surgical field may reach serious and even fatal proportions (Wiener and Peters). There quickly follow icterus, oliguria with hemoglobinuria, and retention of nonprotein nitrogen finally associated with uremia. In patients who develop the full-blown syndrome, death occurs in about 45 per cent of cases in 4 to 18 days. As with the crush syndrome, in those who survive, recovery is heralded with sudden diuresis in about 7 to 14 days. However, not all of the renal functions are immediately fully restored. The blood nonprotein nitrogen may take a month to correct itself completely, and the concentrating ability may remain impaired for several months.

The minimal amount of incompatible blood that has caused a fatal hemoglobinuric nephrosis is in the neighborhood of 350 cc. (Bordley), although as little as 10 cc. may cause symptoms (Eagle). The amount of incompatible blood

PLATE 123 NEPHROSIS OF PROXIMAL NEPHRON: PAROXYSMAL NOCTURNAL  
HEMOGLOBINURIA (MARCHIAFAVA-MICHELI DISEASE)

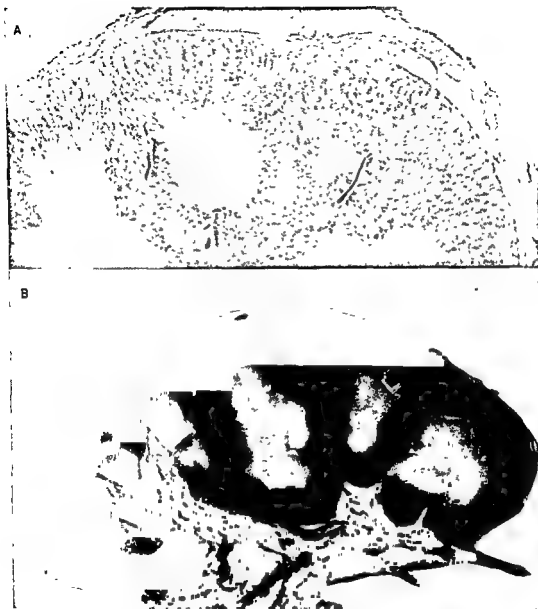


FIG A *Paroxysmal nocturnal hemoglobinuria* showing proximal tubules naturally outlined by deposits of hemosiderin in a slightly enlarged longitudinal section of kidney (Courtesy T. H. Ham, Charles Branch)

FIG B *Prussian blue* reaction on the section pictured above indicates by the darker areas the distribution of the hemosiderin in the cortical tissue

that can be administered without fatality depends on the titer of isoantibodies in the recipient. This titer may be built up through isoimmunization by repeated transfusions so that subsequent transfusions may produce reactions not previously provoked by the same amount of blood. Moreover, certain diseases, such as leukemia, depress the titer so that as much as 1500 cc. of group B blood, for example, may be given to a recipient of group O without effect, according to Wiener and Schacfer. However, there are very few exceptions to the rule that the transfusion of 500 cc. of incompatible blood causes death.

### *Crush syndrome*

In the *crush syndrome*, an individual may be partially buried by debris for several hours. Following his release he may get up, brush himself off and walk away with masked injuries, or, if a limb has been crushed, his traumatic shock responds to treatment. In either case, the symptoms of renal dysfunction begin to manifest themselves in a day or two. The urinary output diminishes, the urine is probably acid and colored by heme pigments (blood hemoglobin or myohemoglobin). The crushed limb swells, and may so dominate the picture as to prompt amputation. Then lethargy, blurred vision, retinitis and hypertension occur along with mounting azotemia and uremia. Complete renal recovery occurs with sudden diuresis in from 7 to 14 days in about 33 per cent of cases at this stage, according to Mallory, in the remainder, death with uremia terminates the picture in this period. In air raids on London during World War II, it was estimated that the crush syndrome accounted for 5 per cent of the casualties. There is a positive correlation between the depth of the shock and the extent of the injuries on the one hand, and the development of hemoglobinuric nephrosis on the other (Mallory).

In addition to the *crush syndrome*, other diseases of muscle lead to hemoglobinuric nephrosis. Acute paralytic myohemoglobinuria is a remarkable recurrent syndrome, characterized by an unusually painful swelling of skeletal muscles, either spontaneously, or after exercise, followed by fever, myohemoglobinuria,

anuria and azotemia. Up to 1943, seven cases had been reported (Bywaters and Dible). Fatality from acute paralytic myohemoglobinuria occurs in a high percentage of the few human cases. The corresponding disease in overexercised and overfed horses (paralytic equine myohemoglobinuria) leads to a mortality between 20 and 70 per cent. At autopsy, the involved necrotic muscles in the animals and in man, have a color and texture resembling fish flesh, and the kidneys are indistinguishable from those of hemoglobinuric or myohemoglobinuric nephrosis. Bywaters and Dible noted the resemblance of the clinical course of acute paralytic myohemoglobinuria to that of fatal porphyria. Apparently a disease similar to myohemoglobinuria is caused in man and cats from the ingestion of fish that have fed on certain cellulose industrial waste from a region in Germany. The condition is known as Haff's disease, or bay sickness. Uteroplacental hemorrhage may also lead to a fatal hemoglobinuric nephrosis.

We have observed still another circumstance in which muscle injury in association with operative shock produced a hemoglobinuric or myohemoglobinuric nephrosis. A 33 year old man was maintained in a knee-chest position for six hours during an operation for removal of a herniated intervertebral disc. Death occurred in anuria and uremia seven days postoperatively. The thigh muscles were acutely necrotic and the kidneys showed hemoglobinuric or myohemoglobinuric nephrosis. No spectroscopic studies on the urine or blood were done.

In other words, a wide range of circumstances and factors leading to necrosis of muscle, including spontaneous or preferably idiopathic myositis, uterine apoplexy, and massive crushing injuries may all be associated with renal changes that are histologically and, to date, physiologically indistinguishable. Precisely what the nature of the common chemical trigger is remains to be determined. The likelihood is that this trigger, which is activated in the syndrome following rapid destruction of muscle, is similar to that set off after incompatible transfusions, after extensive liver damage, during certain infections, and after the use of drugs and hemolytic agents.

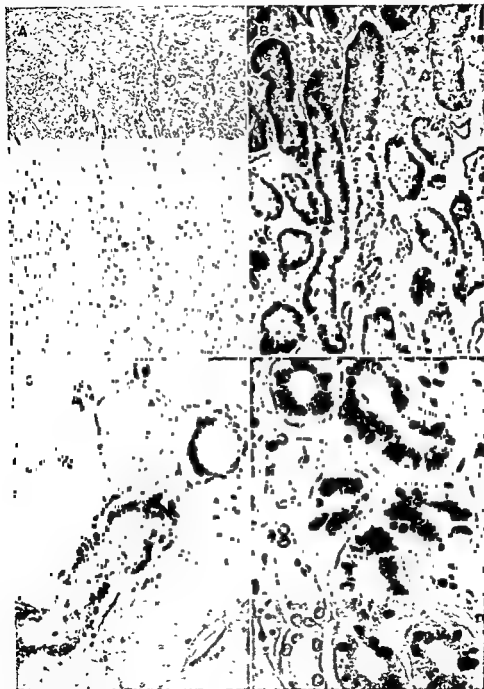


FIG A Paroxysmal nocturnal hemoglobinuria showing distribution of hemouderin in the more darkly staining proximal tubules

FIG C Hemochromatosis with hemouderin in the epithelium of the distal convoluted tubules in contrast to the site of hemouderin deposits after intravascular hemolysis (Perla's stain for ferrocyanide reaction)

FIG B Prussian blue reaction demonstrating large amounts of hemouderin within the epithelium of proximal tubules (Marchisfava-Micheli syndrome)

FIG D Yellowish-brown lipochrome granules may be confused with bilirubin and with the more refractile coarser granules of hemouderin. Their pathogenesis is not clear.



## Pathology of Hemoglobinuric (Lower Nephron) Nephrosis

### Gross Appearance

The kidneys are enlarged, often to between 250 and 350 Gm. each. Their consistency is flaccid rather than tense as from increased intrarenal pressure due to ureteral obstruction. The capsules are easily stripped off their surfaces. The sectioned surfaces are moist and smooth and tend to bulge over the cut edge of the capsule. This tendency of the parenchyma to protrude beyond the capsule has been interpreted as indicative of an increased intrarenal pressure that might be relieved by decapsulation. Evidence in support of this interpretation has recently been advanced by manometric data on intrarenal pressure (Peters). It appears more likely, however, that the occasional beneficial result from decapsulation is more dependent on interference with the renal nerve supply than on the relief of parenchymal tension.

The cortices are widened and pale in contrast to the medullary pyramids which are streaked bright red, not by hemoglobin in the tubules, as some believe, but by the congested vasa recta and peritubular capillaries (plate 127).

### Histologic appearance

It would appear that the abundant material pretty universally available would eliminate any major disagreement as to the facts of the histologic appearance of hemoglobinuric nephrosis. Nevertheless, basic divergence in the simple reportorial descriptions exists. It is acknowledged that the histologic pattern is identical in hemoglobinuric nephrosis following incompatible transfusions, shock, crush or whatever cause. This pattern consists of:

1 Casts of hemoglobin (or a closely related pigmented globin) in the distal convoluted or collecting tubules. In practically all instances sections of medulla reveal casts in the collecting tubules in the vicinity of the pyramidal apex. These casts are usually fairly numerous but are often not sufficient to account for renal insufficiency on the basis of obstruction of nephrons. The presence of a few casts of hemoglobin in the lumens of distal convoluted tu-

bules situated close to glomeruli does not of itself justify the diagnosis of hemoglobinuric nephrosis. This latter condition is found fairly commonly in infectious diseases particularly (Allen and Spitz) and is not responsible for significant renal dysfunction.

The distinction of the brown granular hemoglobinuric cast from casts of myoglobin (presumed to occur with the crush syndrome) can not be made with routine stains. Spectroscopic studies have been applied to blood and urine but the results have not been altogether satisfactory, in part because of the rapidity with which myoglobin disappears from the blood. The renal threshold for myoglobin is 15-20 mg per 100 cc. of plasma in contrast to slightly over 100 mg. per cent for blood hemoglobin. The rate of clearance of myoglobin is about 25 times more rapid than that of blood hemoglobin (Yuile et al.). As stated, the pigment casts of blood hemoglobin and muscle hemoglobin are histologically indistinguishable. Moreover, myohemoglobin, as Millikan points out, is a true hemoglobin, and actually constitutes one fourth of the total hemoglobin of the body. However, there are certain other differences between blood and muscle hemoglobin. These are as follows (Millikan):

(a) The myohemoglobin does not normally circulate but is found in the muscle fibers, unless released by their rupture.

(c) The spectroscopic absorption bands of myo-

to oxygen

(e) Myohemoglobin has only one iron atom per molecule instead of four.

(f) Myohemoglobin is much more resistant to alkali denaturation than blood hemoglobin.

(g) The precipitin reactions are specific for each

Although these differences are unquestionably definite, they do not render inappropriate the application of the term "hemoglobinuric

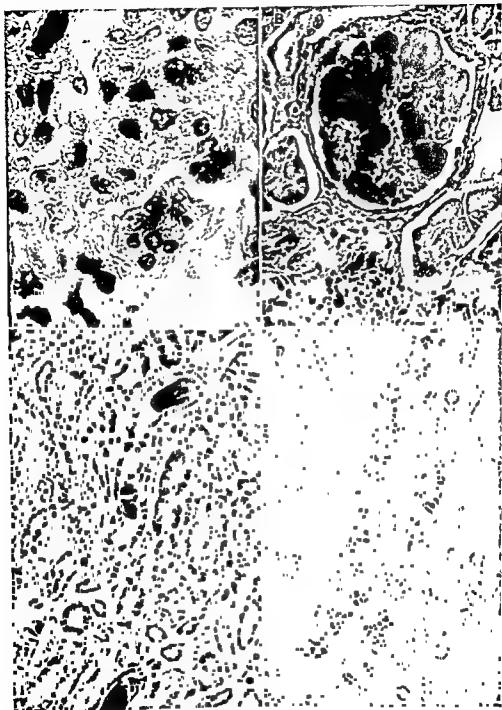


FIG A Malarial pigment in glomerular endothelial cells

FIG B Melanin pigmentation of melanocarcinomatous cells metastatic to glomerulus

FIG C Melanin casts in distal convoluted tubules in a case of melanocarcinoma

FIG D Melanin granules in epithelium of proximal convoluted tubules in a case of melanocarcinoma (unstained section).



FIG. A. *Acute myositis with necrosis and calcification following a crush injury associated with hemoglobinuric nephrosis*

FIG. B. *Kidney of crush syndrome with hemoglobin-like casts, focal interstitial edema and inflammation, and dilatation of Bowman's spaces with protein precipitate*

FIG. C. *Pigment casts (possibly myoglobin) in distal nephron in a case of crush syndrome. Tubular epithelial degenerative changes are present about casts*

FIG. D. *Crystals of hemoglobin in experimental hemoglobinuric nephrosis (Courtesy, Dr Robert Haskhol)*

nephrosis" as applied to the crush and related syndromes (e.g., incompatible transfusions, blackwater fever)

A considerable problem at times is the differentiation of casts of hemoglobin from those of bile in cholemic nephrosis or even, occasionally, from ordinary granular protein casts. In routine sections stained with hematoxylin and eosin, casts of bile are not always as unmistakably green as is often thought, nor are the heme casts always characteristically brown. The Lephène and cyanol stains which make use of hydrogen peroxide and benzidine in the staining of hemoglobin in paraffin sections are not nearly as satisfactory in practice as the literature indicates.

**2. Tubular epithelial change** Because of the belief that the tubular epithelial degeneration in the distal portion of the nephron is the most significant change, the term "lower nephron nephrosis" has been applied to this renal disorder, previously called "hemoglobinuric nephrosis" (Lucké). Degenerative and regenerative changes certainly may be noted in distal convoluted and collecting tubules (plate 128 B). In some instances, however, this change is conspicuous, and in others, with a similar clinical picture in terms of degree and duration, no such tubular damage is observed. In the majority of cases, the degeneration of tubular epithelium is not quantitatively, or even qualitatively, pronounced. Nor is this evaluation of the extent of the tubular damage refuted by the photomicrographs used even by those who place great emphasis, not only on its occurrence, but on the role of such damage in the production of anuria or oliguria. Histologically intact tubular epithelium about the heme casts of hemoglobinuric nephrosis is so common a finding, (plate 128, 129 A) that it appears unlikely that whatever tubular epithelial damage does occur is produced by these casts. As a matter of fact, otherwise similar renal lesions and clinical pictures may occur in the absence of heme casts (Ayer and Gauld, McLetchie, Young). Indeed, some of the most obvious tubular degeneration when it is present, occurs not about the pigment casts but in the region of the protein casts in the distal convoluted tubules.

**3 Interstitial reaction** Focal interstitial ne-

phritis with inflammatory cells and edema is an almost constant feature of fatal hemoglobinuric nephrosis. The interstitial edema is principally cortical, the inflammatory cells occur in foci chiefly at the cortico-medullary junction and in the medulla, although the upper cortex may also be involved. The inflammatory cells are usually lymphocytes, plasma cells and histiocytes, in some instances eosinophilic leukocytes predominate and these do not necessarily represent a reaction to a drug. The suggestion that an allergic element existed in hemoglobinuric nephrosis was made by Kimmelstiel.

**4 Protein casts** Weakly acidophilic, irregularly outlined casts of homogeneous density are often present in the distal convoluted tubules usually of the cortex. As a rule, however, they do not appear to be sufficiently numerous to interfere significantly with renal function, nor is there an obstructive dilatation of the proximal portions of the nephrons in which they are located. In the cases resulting from reactions to sulfonamides, crystals of these drugs may be embedded in the casts. Other crystals closely simulating the structure of acetylated sulfonamides may be found in the kidneys of patients with hemoglobinuric nephrosis who did not receive sulfonamide therapy. These crystals are birefringent, greenish-yellow to blue black, the latter are calcified. Their precise nature is not known, although as we have noted, they resemble the crystals of leucine, and are often found in association with acute, destructive diseases of the liver (plate 134 B).

The distal convoluted tubules with or without their casts may be ruptured, surrounded by inflammatory cells or foreign body granulomas (plate 143 C). The veins at this level (usually arcuate veins), are closely applied to the distal tubules which may herniate into the venous lumens and frequently cause thrombophlebitis (plate 143 A).

**Miscellaneous** Other inconstant features include glomerular ischemia and proliferative glomerulitis, dilatation of the proximal convoluted tubules with loose granular protein precipitate in their lumens, fatty change in the epithelium of the proximal tubules and increase in the size and number of the granular cells of the juxtaglomerular apparatus (according to Goor-

PLATE 127. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRON: BLACKWATER FEVER  
(*P. FALCIPARUM*)



Magnified (14X) gross section of cortico-medullary region of kidney in blackwater fever. The dark streaks of the medulla are really radial peritubular blood vessels rather than tubules filled with casts of hemoglobin. (A F I P. Acc. 37600) Histologic sections in figures A and B, plate 129

PLATE 128. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRON: HEMOGLOBINURIC  
("LOWER NEPHRON") NEPHROSIS



FIG A *Blackwater fever with casts of hemoglobin and associated focal acute interstitial nephritis*

FIG B *Polypoid tubular regeneration of epithelium of collecting tubules in blackwater fever*

FIG C *Hemoglobinuric ("lower nephron") nephrosis caused by sulfathiazole therapy*

FIG D *Hemoglobin casts with associated purulent exudate in collecting tubules in blackwater fever*

FIG E *Hemoglobinuric nephrosis associated with acute yellow atrophy of the liver secondary to poisoning by carbon tetrachloride. In none of the latter three instances (figures C, D, E) is there significant epithelial necrosis*

maghtigh). The occasional dilatation of the proximal tubules (plate 142 B) is attributed to the obstructing heme casts rather than to the coagulum of protein found in the distal convoluted tubules.

*Pathologic Physiology of Hemoglobinuric (Lower Nephron) Nephrosis*

One of the key physiologic problems in need of clarification is the mechanism of oliguria and anuria in hemoglobinuric nephrosis. The point of view generally held (Lucké; Dunn et al., Bywaters and Dible) is that adequate glomerular filtration occurs, but that in its passage down the nephron, the filtrate is reabsorbed across the necrotic tubular epithelium into the peritubular capillaries. This entirely inferential explanation has won general favor because of three attendant circumstances: (1) the direct and brilliant observation by Richards that glomerular filtration is unimpaired in the kidneys of frogs poisoned with mercury bichloride, (2) the widely and uncritically accepted assumption that extensive tubular epithelial necrosis is constant in "lower nephron" or hemoglobinuric nephrosis and (3) the relative paucity of glomerular histologic changes.

In criticism of the use of this evidence, it is suggested, with regard to Richards' observations (assuming the findings in frogs are transferable to man) that mercury bichloride produces an admittedly constantly severe degree of tubular necrosis in contrast to that of hemoglobinuric nephrosis. Moreover, the tubular necrosis resulting from bichloride poisoning affects the proximal and not the "lower nephron," a differentiating fact not prominently cited when Richards' experiment is used as supporting evidence for the hypothesis of "tubular oliguria." Finally, there is actually no positive evidence, even if the tubular basement membrane were stripped of its epithelium, that oliguria or anuria would result from reabsorption of filtrate. One must question the validity of the hypothetical mechanism of passive diffusion which accounts for the complete transfer of the glomerular filtrate across even a naked tubular basement membrane of the distal portion of the nephron. This skepticism is further justified by the presence of oliguria and anuria

in hemoglobinuric nephrosis without pronounced epithelial necrosis. Furthermore, to explain the sudden diuresis which heralds recovery in these patients, it seems necessary to presuppose a correspondingly sudden healing of the tubular epithelium. This manifestly does not hold and could not occur. Nor does the assumption that tubular epithelium in hemoglobinuric nephrosis fails to regenerate until the tenth day appear warranted in view of observations on the more rapid regenerating capacity of epithelium in this and other diseases. It is true that the specific gravity of whatever urine is formed is at a fairly constant level, in the vicinity of 1.010. This fact indicates an incapacity of the tubules to concentrate the glomerular filtrate. A disturbance in tubular concentrating capacity is not necessarily indicative of a total or nearly total transference of fluid from the tubular lumen to the peritubular capillaries. After all, the proximal tubules are chiefly responsible for the concentration of glomerular filtrate, and the epithelium of this portion of the nephron is generally admitted to be structurally intact, as indicated by the term "lower nephron" nephrosis. The fact is that interference with tubular concentrating ability need not imply necrosis of tubular epithelium. Indeed, this function is often not completely restored in cases of hemoglobinuric nephrosis until weeks after organic residua of the disease are gone.

*Mechanism of anuria*

What, then, is the pathogenesis of the oliguria or anuria in hemoglobinuric nephrosis? A diminution or cessation of glomerular filtration seems to be the more plausible answer. However, the proof for this mechanism is as difficult to establish at this time as the tubular reabsorptive concept is vulnerable to refutation. Clearance (Goormaghtigh) and histologic studies (French) suggesting glomerular ischemia do not constitute positive proof. The fact with regard to the histologic demonstration of glomerular ischemia is that, although it may occasionally be observed, many cases simply do not show this glomerular change. Moreover, an equivalent amount of glomerular alteration may be found in cases of acute focal or

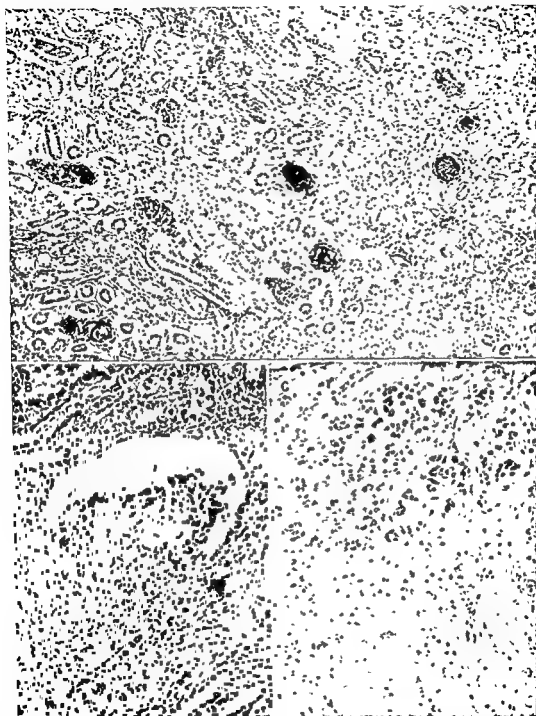


FIG A Hemoglobinuric nephrosis due to reaction to sulfathiazole

FIG B Thrombophlebitis of arcuate vein is found in hemoglobinuric nephrosis of a variety of causes

FIG C Necrosis of anterior lobe of pituitary gland in postpartum transfusion reaction with hemoglobinuric nephrosis





FIG A *Acute hemorrhagic glomerulonephritis* with red blood cells, some laked, in Bowman's space and in distal nephron. The proximal tubules do not contain blood.

FIG C *Erythroblastosis fetalis* with casts of partially laked red blood cells in collecting tubules.

FIG E *Cholemic nephrosis* with bile casts in distal convoluted tubules. Bile casts may be indistinguishable from hemoglobin or myoglobin casts in routine sections and often with special stains.

FIG B *Acute exacerbation of chronic glomerulonephritis* with red blood cells and hyaline casts in collecting tubules.

FIG D *Erythroblastosis fetalis* (higher magnification of figure C). Partially fragmented as well as nucleated red blood cells in collecting tubules.

FIG F. Red blood cell casts in collecting tubules from a case of thrombocytopenic purpura.

acute diffuse proliferative glomerulonephritis without anuria or striking oliguria. However, the experimental observation of glomerular ischemia with stimulation of splanchnic nerves (Bieter), glomerular hyperemia with sectioning of these nerves (Bieter), and the diversion of blood in shock from the kidney to other "more vital" areas, suggest that oliguria and anuria occur in hemoglobinuric nephrosis because so little filtrate passes through the glomeruli. The shock that is the great common denominator of these cases diverts much of the huge proportion of blood that normally circulates through the glomeruli (25 per cent of the cardiac output) into other organs, as stated previously. There is beginning to accumulate considerable doubt that, in man at least, this divergence is effected by shunting the blood away from the cortical glomeruli to the juxtamedullary glomeruli. The finding of congested outer cortical glomeruli lends support to the doubt. In other words, there appears to be an over-all reduction in renal blood flow in hemoglobinuric nephrosis.

Although those observers who postulate the tubular origin of oliguria and anuria in hemoglobinuric nephrosis stress the common and important role of shock, they do not at the same time, incorporate in their concept some of the striking physiologic effects produced on the glomeruli by shock. For example, Lauson, Bradley and Cournand find that the glomerular filtration and effective renal plasma flow are significantly and consistently reduced in proportion to the degree of shock, and that the degree of oliguria reflects the rate of glomerular filtration which, in turn, is related to a reduction in renal blood flow. The rapid—if only occasional—response to sympathetic block by the local or intravenous use of procaine would seem to be additional evidence of a vasoconstricting mechanism as a cause of the anuria, rather than tubular backflow (Fries, Langerson et al.)

#### *Auxiliary pathogenetic factors*

It is entirely likely that auxiliary factors contribute to the renal embarrassment. The heme or related pigment casts probably do not usually play a significant role in the dysfunction, but, on occasion, they are so abun-

dant and so compact in the strategically located collecting tubules that they may infrequently produce the physiologic equivalent of a partial internal hydronephrosis (plate 142 B). That this is not common is attested to by the absence of a mass of hemoglobin casts piled loose into the urine at the time of diuresis and recovery.

The interstitial edema and interstitial infiltration may in some instances be of appreciable degree, and may further compromise renal function. The thrombophlebitis and tubular coagula rarely seem to be sufficiently abundant to interfere significantly with function.

Because of the conspicuousness of hemoglobinuria and of the heme casts in the histologic sections of many of these kidneys, much experimental effort has been devoted to a determination of toxicity of hemoglobin and myoglobin and related compounds. Pure hemoglobin as well as pure myoglobin circulating in the blood stream is not toxic for humans (Anderson et al., Bing). Nor is this fact altered by rendering the urine acid as is demonstrated by patients in hemolytic crises from paroxysmal nocturnal hemoglobinuria, who have been given ammonium chloride without the development of hemoglobinuric nephrosis. This phenomenon is of interest because it has been assumed that the acidity of the contents of the lower nephron is responsible for the precipitation of the heme casts, an assumption that has led to widespread, often excessive, therapeutic use of alkali in cases of hemoglobinuric nephrosis. Actually, fatalities from incompatible transfusions or blackwater fever may occur with persistently alkaline urine. Nevertheless, it is still considered good practice to keep the urine alkaline. Some observers have suggested that the tubular injury is a requirement for the precipitation of the heme casts (Yule, Steinman, Hahn and Clark). However, heme casts are noted in the kidneys with hemoglobinuric nephrosis in the absence of associated histologically evident tubular damage.

When the many disparities are taken into account, there remains the common impression that it is not the hemoglobin or myoglobin, *per se*, that causes the renal dysfunction. Other potentiating, or synergistic factors may exist

in the form of urinary pH, oliguria, shock, vasoconstricting agents, adenosine phosphates, porphyrins, or porphyrin-like substances, and nephrotoxic chemicals produced as a result of hepatic dysfunction. Even the ferrihemate (or ferrihemate and albumin, i.e., methemalbumin) is considered by Anderson to exert its effects on the kidney in blackwater fever, not by its direct damage to the nephron but by its vasoconstrictive and thrombogenic effects. The nephrotoxic effects of hepatic origin are suggested by the high incidence of hemoglobinuric nephrosis in association with acute yellow atrophy, particularly following carbon tetrachloride poisoning. However, of all the factors potentiating the hemoglobinemia or myohemoglobinemia, the shock, with its attendant renal vasoconstriction and extrarenal diversion of blood flow, seems of first line importance.

### Terminology

It is not especially important whichever name is given to the renal disease under discussion, so long as the disease is understood. The term "lower nephron nephrosis" (versus hemoglobinuric nephrosis) has in recent years achieved considerable popularity. Nevertheless its following limitations ought to be set down.

1. There are many "nephroses" of the lower nephron, including those due to myeloma, gout, sulfonamides, nephrocalcinosis (secondary to alkalosis, bony lesions and hyperparathyroidism), uric acid, and hepatic diseases (cholemic nephrosis). Each of these conditions is a lower nephron nephrosis in a sense as complete as, or more definitive than, hemoglobinuric nephrosis.

2. The proximal portion of the nephron is also occasionally involved with focal necrosis in hemoglobinuric or "lower nephron nephrosis." McManus states that there is a reduction in alkaline phosphatase in the proximal nephron in hemoglobinuric nephrosis and so suggests that "lower nephron nephrosis" is a misnomer.

3. The necrosis of the tubular epithelium of the distal nephron is often inconspicuous.

4. The renal dysfunction cannot be convincingly explained on the basis of the necrosis of the distal tubular epithelium, or of the casts in the lower part of the nephron. Hence, the designation "lower nephron nephrosis" focuses undue attention on the distal nephron from the point of view of functional and therapeutic investigations.

5. Casts of hemoglobin or the closely associated myohemoglobin are, after all, the conspicuous and constant feature of hemoglobinuric nephrosis, or so-called "lower nephron nephrosis." The very few cases of so-called "lower nephron nephrosis" in which such pigment casts are absent, as in alkalosis, need to be re-evaluated in the manner indicated in this section.

For these reasons chiefly, the term "lower nephron nephrosis" seems not to have advantages sufficient to displace the pre-existing name, "hemoglobinuric nephrosis."

### CHOLEMIC NEPHROSIS

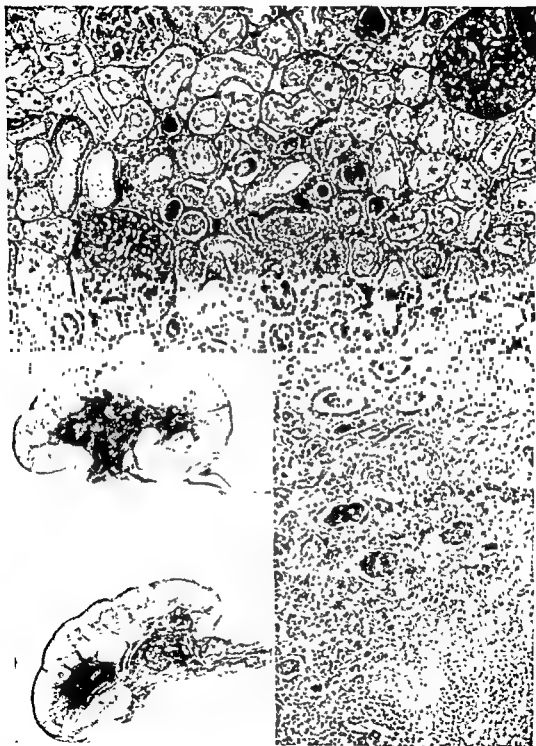
#### Introduction

The term "cholemic nephrosis" has come to have various and confusing connotations. Unlike some other unhappily chosen names of renal diseases, the difficulty with "cholemic nephrosis" is not that it fails to signify the particular renal structure at fault, but that the functional significance of this broad and ill-defined histologic entity has not been thoroughly clarified. Another limitation of the use of the term "cholemic" is that occasional cases may occur in the absence of jaundice, although in the presence of hepatic damage.

To the clinician as well as to the pathologist, one form of cholemic nephrosis is the more nebulous renal component of the *hepatorenal syndrome*. The hepatorenal syndrome refers to several clinical variations of the postoperative course of patients who have had an opera-

FIG. A. Hemolyzed blood in Bowman's space and in distal tubules following accidental ingestion of one tablespoonful of hydroquinone with pyrogallie acid. Death in 48 hours.

FIG. B. Hemorrhage into calyces and pelves in aplastic anemia. Incidentally the bulk of the pelvic hematoma may simulate neoplasm by pyelography.



(Legends on facing page.)

PLATE 132. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRONS: CHOLEMIC NEPHROSIS  
(CARBON TETRACHLORIDE)

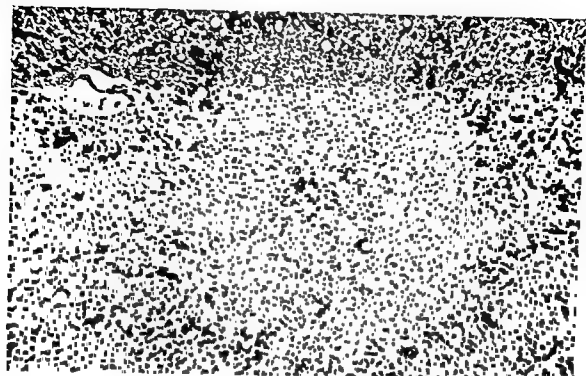


FIG A Acute yellow atrophy due to carbon tetrachloride poisoning. The necrosis is central and is associated with moderate fatty change.

FIG B Kidney from a case of carbon tetrachloride poisoning with cholemic nephrosis.

FIG C Kidney from a case of cholemic nephrosis due to carbon tetrachloride poisoning with bile casts in the distal nephron and mild osmotic nephrosis in the proximal tubules.

tion done on some part of the biliary system. Stated summarily, these patients expire early (in the first 2 or 3 days) with icterus, coma and hyperpyrexia, or late (7 to 14 days) in their postoperative period with fever, interference with biliary drainage and with what is regarded as hepatic and renal insufficiency, including oliguria and azotemia. In the early deaths, no organic renal changes are reported either in man or dog (after ligation of the hepatic artery) (Sutton), in deaths occurring later, cholemic nephrosis is found. There is no doubt that a great number of diagnoses of hepatorenal syndrome would not be made if a postmortem examination were done. The reason is that many cases that are called "hepatorenal" syndrome clinically, are found at autopsy to have clear cut organic reasons for death which were not previously suspected. These causes include hemoperitoneum, bile peritonitis, ligation of the hepatic artery with hepatic infarction, or some other unforeseen complication. But even when these are subtracted there remains a significant number of instances that must be retained even by the pathologist in the category of hepatorenal syndrome. In these cases, there is invariably jaundice, usually severe, with the clinical picture closely akin to hemoglobinuric (lower nephron) nephrosis.

#### Pathology

With this orientation, is it then possible to define cholemic nephrosis pathologically? In any event, the individual pathologic changes are these:

Grossly, the kidneys are swollen and diffusely bile stained. The diffuse green coloration may not be completely appreciated until after the tissue has been fixed in formalin. Except for the icteric tinge, the sectioned surface resembles that of the kidney with hemoglobinuric nephrosis, it is moist, the cortex is widened and sharply delimited from the medulla and the medulla is radially streaked with congested vessels (plate 132 B).

Histologically, the changes are primarily tubular. These changes consist of

- 1 granular bile staining of the epithelium of the proximal portion of the nephron down to the loops of Henle (plate 134 D),

- 2 gross hydropic vacuolization of the cytoplasm of cells of the proximal convoluted tubules without conspicuous nuclear change (plate 134 A, 134 B) similar to that seen in cases of ulcerative colitis (plate 108 B),
- 3 infrequently, frank necrosis of epithelium with evidence of regeneration (plate 133) within proximal convoluted tubules;
- 4 bile casts, occasionally indistinguishable from hemoglobin casts, in the distal convoluted collecting tubules (plate 134 A),
- 5 focal interstitial infiltration of lymphocytes, histiocytes and a few plasma cells,
- 6 yellowish brown spherical amorphous and crystalline bodies usually in the distal convoluted tubules (plate 134) but occasionally definitely the proximal tubules (plate 135 F).

The amorphous bodies are homogeneous, about 20-30 microns in diameter and are almost always birefringent; these are strongly reminiscent of the "starch"-like bodies described by Councilman in the kidneys of yellow fever as found by us often in the kidneys associated with any form of severe acute hepatitis, acute yellow atrophy, viral or chemical. They are crystalline, yellowish green, spherical bodies of the same size as the amorphous ones, and constantly birefringent, and have radial lines so as to simulate the crystals of acetylsalicylic acid or sulfathiazole (plates 137, 138). These bodies resemble also leucine crystals and adenine phosphate, but their accurate identification awaits further study. The crystals, as the amorphous bodies, are found in cases of severe acute hepatitis, and in jaundice secondary to calculi or neoplasm obstructing the common duct.

Any one, or a combination of the above findings may be present with hepatic disease. Obviously, the amount of dysfunction will vary with the type and severity of the histologic change in the kidneys. In other words, mere bile-staining of epithelium and scattered bile casts need not cause significant renal dysfunction.

It is not always possible to know from the histologic sections alone what severity of renal dysfunction had existed. As a rule, however, the more closely the over-all histologic picture

approaches that of hemoglobinuric nephrosis—substituting bile casts for hemoglobin casts—the more easily can it be suspected that corresponding renal dysfunction had occurred.

### *Pathologic Physiology*

In view of the intimate association of hemoglobinuric nephrosis and other renal damage with disease of the liver as in carbon tetrachloride and mushroom poisoning, sulfonamide intoxication (Kuzma and Polley), and infarct of the liver, there can be no doubt of a pathogenetic relationship between hepatic disturbances and renal changes. What the precise mechanism is, remains to be clarified. It is a known fact, however, that an abnormal aminoaciduria may occur with severe damage of the liver, and that leucine, tyrosine, and other amino acids are excreted. Experimentally, renal tubular damage can be produced with serine, cystine, lysine, arginine, aspartic acid, histidine, and tryptophane (Morehead et al., Cox et al., Newburgh and Marsh, Lillie). Whether or not such an aminoaciduria plays a role in the renal damage in humans is still to be proved. Recently it has been postulated that the acutely damaged liver is vitally concerned with the maintenance of the balance of circulating vaso-excitatory and vaso-depressive substances, and that a disturbance in this balance causes renal dysfunction of the types noted in the hepato-renal syndrome.

## **SULFONAMIDES**

### *Introduction*

The effect of the sulfonamides on the kidney constitutes the most frequent of the serious untoward responses to this important group of drugs. The problem of establishing the basis for a given renal reaction in humans, however, is often hopelessly tangled by the large number of possibly related variables of which transfusions, shock, infections and accompanying allergies are the significant ones. The problem is further

complicated by the fact that each of these variables alone may be responsible for the types of inflammatory lesion also attributable to the sulfonamides. The following outline lists the renal lesions that are produced by sulfonamides.

### *Renal reactions to the sulfonamides:*

- Obstructive calcinosis
  - Intrarenal
  - Pelvic and ureteral
- Inflammatory
  - Nephrosis
    - Necrotizing nephrosis
    - Hemoglobinuric nephrosis
  - Interstitial nephritis
    - Diffuse
    - Focal
  - Acute glomerulonephritis
    - Diffuse
    - Focal
  - Acute necrotizing pyelitis
  - Periarteritis nodosa

The conditions listed above may occur individually or in combination. There is nothing diagnostic about most of these lesions. Except in the obvious obstructive uropathies, it is usually the clue from the gratuitous presence of a few crystals of sulfonamides, certain distinctive granulomatous reactions, and a convincing clinical history of the administration of the drug and concomitant effects (for example, skin rash) that leads to the inferential conclusions concerning pathogenesis.

### *Obstructive Calcinosis*

Obstructive calcinosis has been observed experimentally following the administration of prontosil, sulfapyridine (Gross et al., Antopol and Robinson, Van Dyke et al.), sulfathiazole (Van Dyke et al., Climenko and Wright), sulfamethylthiazole, sulfadiazine, and sulfaguandine, concretions were not noted with sulfanilamide experimentally. The sulfapyridine produces obstructive concretions more commonly than sulfathiazole (Van Dyke et al.)

FIG A. Distinctive hydropic vacuolization seen especially in cholemic nephrosis of whatever cause and also in ulcerative colitis. The evidence of degeneration in the nonvacuolated epithelial cells of the proximal tubules is also noted.

FIG B. Bile casts with degeneration of epithelium of the distal tubules are seen in this case of cholemic nephrosis.

FIG C. Bile casts in the distal nephron with necrosis and desquamation of epithelial cells are seen (cholemic nephrosis).

PLATE 133 NEPHROSIS OF PROXIMAL AND DISTAL NEPHRON: CHOLEMIC NEPHROSIS  
(CARBON TETRACHLORIDE)



(Legends on facing page)





FIG A. Dense bile casts and crystals (arrow) in distal nephron in a case of poisoning with carbon tetrachloride

FIG C. Cholemic nephrosis following obstruction of common bile duct by a carcinoma of the head of the pancreas, with bile casts, anisotropic spherical crystals (possibly leucine) (arrows) and destruction of epithelium of distal tubules

FIG B. Cholemic nephrosis (carbon tetrachloride) showing spherical crystals, possibly leucine (black), proteid cast in the distal tubule, oncotic as well as destructive vacuolization in the proximal tubules

parently of bile pigment, are in the epithelium.

PLATE 135. NEPHROSIS OF PROXIMAL AND DISTAL NEPHRON: CARBON TETRACHLORIDE  
FAT NEPHROSIS (PROXIMAL COMPONENT)



FIG. A Basal vacuolization formed by fat in cells of proximal convoluted tubules in a case of acute yellow atrophy due to carbon tetrachloride (A.F.I.P. Acc. 104604)

FIG. B Sudan III stain of kidney illustrated in figure A

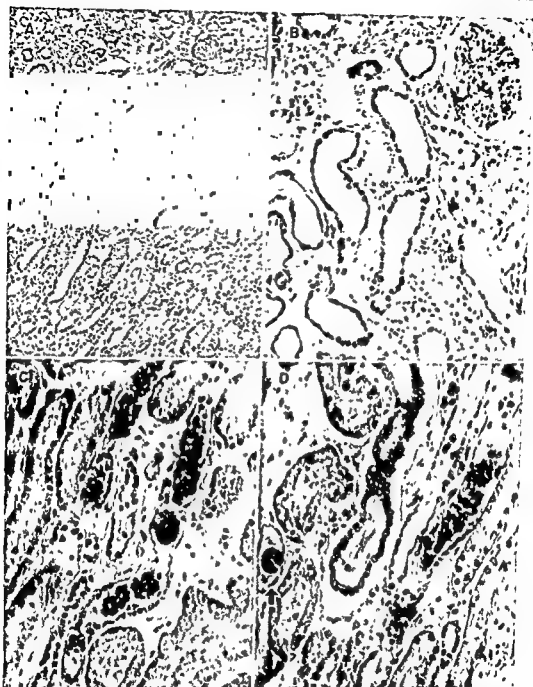


FIG A Hemoglobinuric nephrosis (casts of hemoglobin in distal tubules) in a case of carbon tetrachloride poisoning

FIG B Focal interstitial nephritis with edema and inflammation in carbon tetrachloride poisoning

FIGS C AND D Alkalotic calcification in distal convoluted tubules resulting from the vomiting so common in carbon tetrachloride poisoning. Figure D shows also one of the spherical crystals (arrow) often seen in association with acute hepatic degeneration

PLATE 137. NEPHROSIS OF DISTAL NEPHRON\* SULFONAMIDES, SULFAPYRIDINE  
CRYSTALS

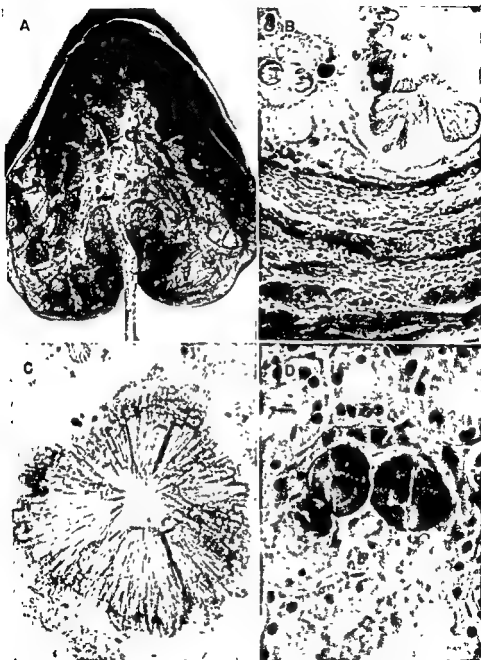
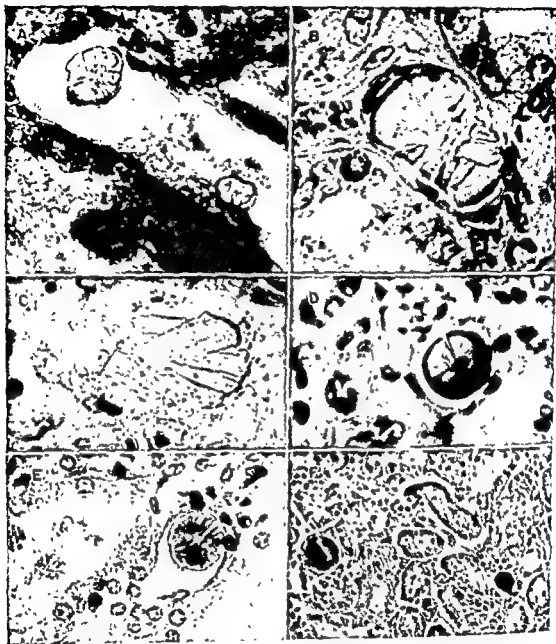


FIG. A. *Sulfapyridine lithiasis in renal pelvis and ureter. This patient manifested pain, hematuria, and dyspnea, but no renal insufficiency. (Case of Schifrin and Kelson.)*

FIGS. B AND C. *Acetylated sulfapyridine crystal*

FIG. D. *Birefringent crystals, possibly leucine, characteristic of acute hepatitis of many varieties. These crystals may be easily confused with the sulfonamides.*

PLATE 138. SULFADIAZINE TOXICITY: APPEARANCE OF  
CRYSTALS IN SECTIONS OF KIDNEY



FIGS A TO D. *Sulfadiazine crystals in the lumens of distal convoluted tubules*

FIG. F *Leucine (?) crystals in kidney associated with a large infarct of the liver. They occur also in acute yellow atrophy caused by a variety of agents*

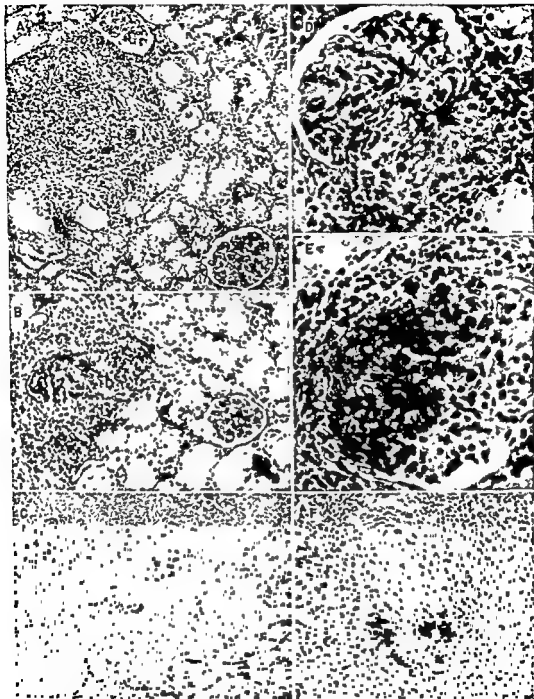


FIG. A. Acute necrotizing glomerulitis due to sulfathiazole. Two normal glomeruli are included in the section.

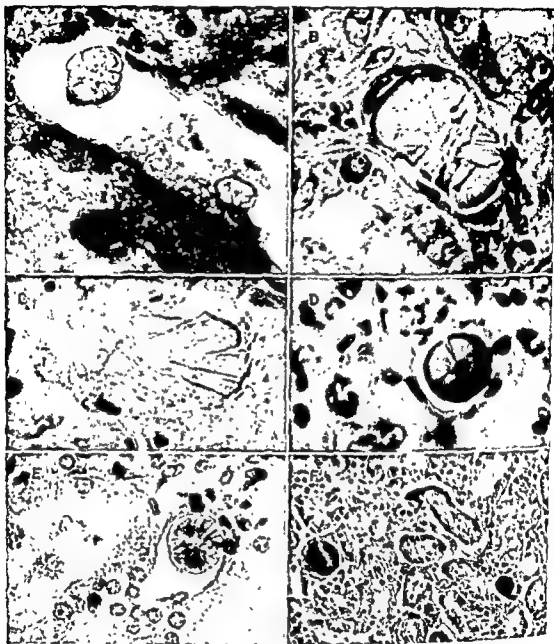
FIG. B. Acute focal exudative glomerulitis and periglomerulitis due to sulfathiazole.

FIG. C. Acute focal exudative glomerulitis and periglomerulitis due to sulfathiazole.

FIGS. D AND E. Acute focal glomerulitis (sulfathiazole) indistinguishable from focal endocarditis glomerulitis.

FIG. F. Acute renal arcuate arteritis due to sulfathiazole, indistinguishable from that of periarteritis nodosa.

PLATE 138. SULFADIAZINE TOXICITY: APPEARANCE OF  
CRYSTALS IN SECTIONS OF KIDNEY



FIGS A TO E. *Sulfadiazine crystals in the lumens of distal convoluted tubules*

FIG F. *Leucine (?) crystals in kidney associated with a large infarct of the liver. They occur also in acute yellow atrophy caused by a variety of agents*

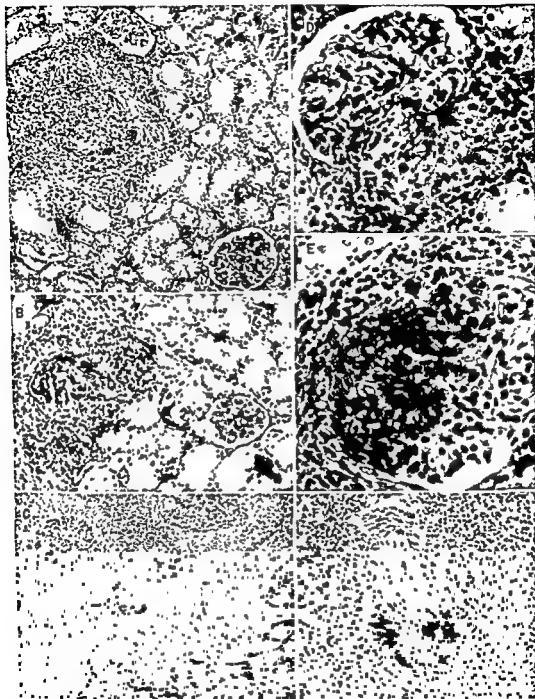


FIG. A. Acute necrotizing glomerulitis due to sulfathiazole. Two normal glomeruli are included in the section.

FIG. B. Acute focal exudative glomerulitis and periglomerulitis due to sulfathiazole.

FIG. C. Acute focal exudative glomerulitis and periglomerulitis due to sulfathiazole.

FIGS. D AND E. Acute focal glomerulitis (sulfathiazole) indistinguishable from focal endocarditic glomerulitis.

FIG. F. Acute renal arcuate arteritis due to sulfathiazole, indistinguishable from that of periarteritis nodosa.



presumably because of the relative insolubility of the acetylated sulfapyridine of which the calculi are composed.

In humans, crystals of the various sulfonamides are found commonly within the parenchyma but obstructive concretions of sulfonamides, such as are illustrated in plate 137 A, are found relatively rarely in the pelvis or ureter. Some observers attribute the infrequency of this finding to the calculi having been washed out in the urine. Their disappearance by this route would hardly seem to be an adequate explanation to account for their rarity at autopsy. The conclusion is that extraparenchymal obstructive calcinosis from sulfonamides is an unusual complication.

#### *Intrarenal Calcinosis*

The intrarenal deposition of sulfonamide crystals is a common occurrence. The crystals are noted frequently, notwithstanding the partial solution of the crystals that occurs in the process of preparation and staining of paraffin sections. The crystals are found in the distal convoluted tubules (plate 139) and only exceptionally in the proximal convoluted tubules (plate 145 C). These crystals may be confused particularly with those seen in the kidney in association with acute hepatitis or hepatic necrosis (plate 137 D), and in some instances may indeed be those very crystals in view of the common association of liver damage in 37 per cent of cases of serious renal complications from sulfonamides (Kuzma and Polley). Sulfonamide crystals may also be mistaken for the crystals of calcium oxalate precipitated in the proximal tubules after the ingestion of ethylene glycol (antifreeze). The calcium deposits in the distal tubules as a result of alkalosis or metastatic calcification usually offer no serious differential diagnostic problem.

Before concluding that intratubular crystals are responsible for renal insufficiency by obstruction of the tubular outflow, evidence of backpressure in the form of internal hydronephrosis (dilated tubules and Bowman's spaces) should be required. In point of fact, such dilatation is rarely caused by intrarenal deposits of sulfonamides. In other words, renal shutdown in the presence of parenchymal crys-

tals of sulfonamides is usually due to associated hemodynamic or inflammatory reactions rather than primarily to tubular obstruction.

#### *Inflammatory Reaction to Sulfonamides*

##### *Nephrosis*

The renal reaction to the sulfonamides that is of most concern, both because of its frequency and its gravity, is hemoglobinuric nephrosis. It may follow the administration of any of the sulfonamides. There may be no difference in the clinical or histologic picture of hemoglobinuric nephrosis caused by the sulfonamides from that previously described and caused by incompatible transfusions and the many other agents or conditions. In some instances, a hint of a sulfonamide etiology is based on the finding of sulfa crystals, often embedded in irregular protein casts in the distal convoluted tubules (plate 143 B). The presence of interstitial giant cell granulomas (plate 143 C, 144 A) is an additional suggestion of a reaction to sulfonamides. Eosinophilic leukocytes within the interstitial infiltrate also is presumptive but far from conclusive evidence of an allergic reaction, possibly to sulfonamides.

Infrequently vacuolization, degenerative changes and actual necrosis of the epithelium of the proximal convoluted tubules occur after sulfathiazole therapy with as serious dysfunction as in hemoglobinuric nephrosis. One such example is illustrated in plate 140 B, and appears to correspond to the description of another case (More et al.) in which sulfathiazole was used.

##### *Interstitial nephritis*

Acute diffuse interstitial nephritis of clinical and histologic types identical with those associated with various septic states occurs infrequently after sulfonamide therapy (plate 141). Of more distinctive histologic appearance, are the examples of focal granulomatous interstitial nephritis described by Lederer and Rosenblatt, as well as others, and characterized by giant cells, various mononuclear cells, eosinophilic and neutrophilic leukocytes, and necrosis. These granulomas may occur in other organs including lungs and bone marrow. They are not a direct reaction to the sulfonamide

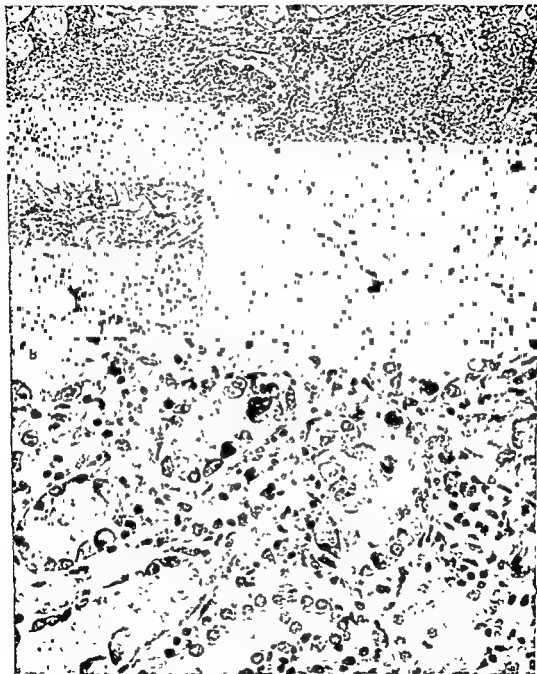


Fig. A *Acute diffuse exudative glomerulonephritis* attributed to sulfapyridine. The intense exudation of polymorphonuclear leukocytes is present in the periglomerular lymphatics as well as in the glomeruli themselves.

Fig. B *Proximal and distal tubular degeneration and regeneration* in reaction to sulfapyridine.

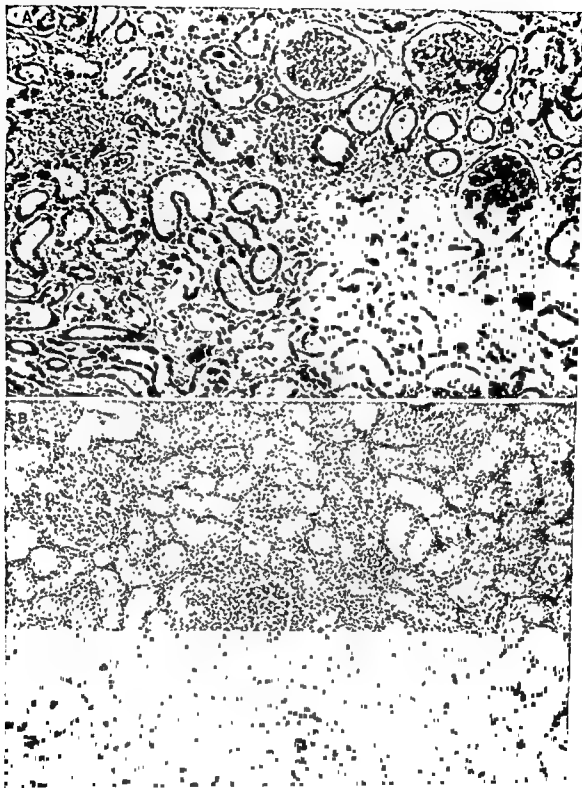


FIG A *Focal interstitial nephritis with marked edema due to sulfathiazole*

FIG B *Acute diffuse interstitial nephritis due to sulfathiazole*

crystals but apparently represent an allergic response

### *Acute glomerulonephritis*

It is not generally appreciated that acute diffuse glomerulonephritis and acute focal glomerulonephritis may represent one of the responses to the sulfonamides. This statement is made with the awareness, previously indicated, of the conflicting possibility that the glomerular reaction may be the result of the original infection for which the sulfonamide was given. This possibility was taken into full account when the cases illustrated in plates 139 and 140 were chosen as examples of glomerulonephritis caused by sulfonamides. The focal glomerulitis illustrated in plate 139 A is characterized by the same type of granulomatous nonbacterial inflammation that is present in the granulomatous interstitial nephritis, and in the granulomatous arteritis attributed to the sulfonamides or allergic responses (plate 237).

### *Necrotizing pyelitis*

Acute hemorrhagic necrotizing calycitis, pyelitis, and ureteritis have been observed occasionally following sulfapyridine (Sadusk et al., Koletsky and King) and sulfathiazole therapy. The case illustrated in plate 147 with hemorrhagic necrotic pyelitis, and ureters obstructed by hemorrhagic exudate admixed with scattered crystals, followed treatment with sulfathiazole. In one case (Kutzenstein and Winternitz), the necrosis caused rupture of the pelvis.

### *Periarteritis nodosa*

The emphasis placed by Rich on the role of sulfonamides in the production of vascular lesions indistinguishable from those of periarteritis nodosa has since led to at least a preliminary search of sulfonamide etiology in all cases of periarteritis nodosa. The evidence is convincing that such lesions may follow the development of hypersensitivity to the sulfonamides with fatal results. As mentioned, a peculiar form of necrotizing granulomatous arteritis (plate 237), not unlike the granulomatous reaction previously described, may be observed

in patients with altered reactivity to sulfonamides.

### *Summary of Renal Reaction to Sulfonamides*

With the increasing use of sulfonamides, evidence has been accumulated of a wide variety of forms of renal damage related directly to the use of these drugs. The types of change include.

- 1 acute focal or diffuse interstitial nephritis,
- 2 acute focal or diffuse glomerulonephritis,
- 3 hemoglobinuric nephrosis,
- 4 focal necrotizing nephrosis,
- 5 hemorrhagic necrotizing pyelitis,
- 6 necrotizing arteritis, and
- 7 the obstructive deposition of masses of crystals of the sulfonamides

There is no constant relationship between the amount of the drug administered and the severity of the renal damage, nor is there a relationship, necessarily, between the severity of the damage and the numbers of crystals observed in sections. This latter impression is not altered by the fact that the crystals have a tendency to be dissolved both in the process of fixation with formalin and in the preparation of paraffin sections.

The renal lesions may be associated with changes in other organs affected by the sulfonamides. These include interstitial eosinophilic myocarditis, diffuse necrotizing arteritis simulating periarteritis nodosa, purulent granulomatous necrotic foci in the lungs, liver, spleen and bone marrow, acute yellow atrophy of the liver, a variety of other changes in the bone marrow, focal necrosis of lymph nodes, encephalomyelitis, and several types of cutaneous rashes. On the other hand, isolated renal lesions do not preclude the possibility of sulfonamides being the offending agent. The pathogenesis of sulfonamide toxicity remains to be clarified, but the evidence to date strongly suggests an allergic factor in which sulfa drugs play the part of haptens.

Attempts to prevent or minimize the precipitation of sulfonamide crystals and the formation of concretions have been made, not only by the alkalinization of the urine, and the dangerous and dubiously effective forcing of fluids, but also by the simultaneous use of



FIG A Hemoglobinuric (lower nephron) nephrosis due to sulfathiazole the epithelium of the collecting tubules containing the casts is not appreciably altered

FIG B Tubular dilatation in a case of hemoglobinuric nephrosis due to sulfathiazole This degree of dilatation is not common in hemoglobinuric nephrosis



FIG. A Thrombophlebitis of arcuate vein in hemoglobinuric nephrosis due to sulfathiazole, a common finding in this condition

FIG. B Thrombophlebitis in reaction to sulfathiazole. The necrotic distal tubules containing the hyaline casts lie directly against the endothelium of the vein and thereby thrombosis is facilitated (Case of hemoglobinuric nephrosis)

FIG. C Sulfathiazole toxicity with giant cell granulomas about a partially degenerated tubule containing a hyaline cast

mixtures of sulfonamides (Lehr). The thought behind such combinations of drugs is that they would preserve or even enhance the antibacterial action and at the same time inhibit the formation of crystals because of the diminished concentration of any one drug in the solution administered. The criticism leveled at this procedure is that, while it may lessen the chances of the formation of crystalline precipitates, it may promote the tendency to allergic reactions by virtue of the exposure to multiple allergenic drugs. This latter danger seems the far more important one to avoid.

#### POISONING FROM HYDROQUINONE-PYROGALLOL (PHOTOGRAPHIC DEVELOPER)

The crystals used as a reducing agent in photographic developing fluid, and used also in the fur industry, have caused fatalities through accidental ingestion. In one instance, the crystals were mistaken for epsom salts; a tablespoonful was swallowed, and death ensued in 48 hours. The composition of the material is 80 per cent hydroquinone, 20 per cent *p*-methylaminophenol sulfate and pyrogallol. The pyrogallol (trihydric phenol,  $C_6H_2(OH)_3$ ) is a well known destructive agent of red blood cells, and is employed for this property in the performance of routine chemical tests, and in the bacteriologic laboratory to create an anaerobic atmosphere. It converts hemoglobin into methemoglobin. Poisoning causes chills, vomiting, diarrhea, cyanosis, anemia, jaundice, circulatory collapse, oliguria and anuria, and death from the combined multiple effects usually in a few days.

The renal picture consists of the presence of hemolyzed blood throughout the nephron, from the very much dilated Bowman's space to the collecting tubules. These homogeneous casts of hemolyzed blood should be easily distinguished from the granular, heme casts by their thin, homogeneous, pale, and also serous appearance, as if the hemolyzed blood had been diluted and escaped into the urine, coloring pink whatever it contacted on its way. No significant tubular degeneration or other noteworthy change is present (plate 131 A).

#### VON GIERKE'S DISEASE

The entity known as glycogen storage disease, hepatonephromegalia, glycogenemia, thesaurosis glycogenica, or more commonly, von Gierke's disease, was first described by E. von Gierke in 1929. The disease occurs almost exclusively in infants, and the essential clinical findings are hepatomegaly, cardiomegaly, nephromegaly, flattened glucose tolerance curve, generally asymptomatic hypoglycemia and acetoneuria. Cerebral symptoms have also been described (Kimmelstiel).

The same organs are not involved in each case and the degree of their involvement varies from case to case. To this extent, the signs and symptoms are different in the small number of cases thus far described. The essential histologic picture is that of glycogen disposition so excessive as to cause marked enlargement of the organs. The liver may be enlarged three to four times and the kidneys to fully twice normal weight. In the liver, the glycogen is in the parenchymal cells; in the heart, the individual fibers may be enormously ballooned out into a network by the glycogen. Glycogenic enlargement of the myocardium may be focal and may present as a tumefaction which in the past has been mistaken occasionally for rhabdomyosarcoma (plate 148 C). In the kidney, the site of deposition of the glycogen is variously reported in any or all portions of the nephron including the glomerular tuft, Bowman's space, the parietal epithelium, the epithelium of the proximal, distal and collecting tubules, as well as the lumens of the tubules. In other words, the glycogen is not confined to the region of the loops of Henle as in diabetes mellitus nor are the vacuoles nearly as large as those of diabetes mellitus (plate 108 C, 148 A). The analysis of the kidneys in von Gierke's case by Schonheimer revealed them to contain 6.53 per cent of glycogen, whereas the maximum value found in the kidney in diabetes mellitus was 1.64 per cent (Popper and Wozasek). The glycogen deposits do not cause renal insufficiency. Glycogen has been found also in the brain, in the endocrine glands, in muscles, in the pancreas and in blood vessels.

There is no evidence that the glycogen is



FIG. A. Giant cell granulomas about distal convoluted tubules in sulfathiazole toxicity.

FIG. B. Calcification of distal nephron in a case of sulfathiazole toxicity in the absence of alkalosis.



A

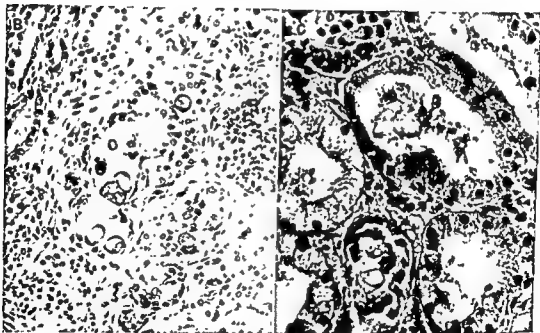


FIG A Doubly refractile crystals in kidney following oral administration of Sulfasuxidine. The crystals of other sulfonamides are also doubly refractile. Despite the relative lack of reabsorption of Sulfasuxidine, apparently a sufficient amount may be absorbed on occasion to produce the crystalline deposits in the kidney shown above.

FIG B Crystals in distal tubules following use of sulfasuxidine.

FIG C Crystals in proximal convoluted tubules following the use of Sulfasuxidine. This patient was also given ascorbic acid, of which a theoretical intermediate product of metabolism is calcium oxalate.

abnormal in composition or that there is a significant excess of it in the blood. Urinary amylase has been found increased in some cases. The supposition is that there is an enzymatic disorder of glycogenolysis at fault. Renal phosphatases, both acid and alkaline, show no abnormality (Wachstein) (plate 148 B).

## MULTIPLE MYELOMA

### Introduction

Although renal insufficiency is a common cause of death in patients with multiple myeloma (43 per cent according to Adams et al.), there is much difference of opinion as to exactly what renal lesions are present. In part the difficulty arises from the fact that multiple myeloma is a disease of the latter decades of life, in which age groups renal lesions occur (for example, arterial and arteriolar nephrosclerosis, pyelonephritis) that are independent of the myeloma. In addition, myelomatous disease of the vertebral column may involve the spinal cord so as to lead to a "cord bladder" and consequent pyelonephritis. Moreover, about 6 per cent of patients with myeloma develop amyloidosis. As a rule, however, the amyloidosis is of the atypical type or "para-amyloidosis" in which the amyloidotic change is found in unusual sites, such as tongue, heart, skin, bone and joints rather than in the liver, spleen and kidneys. Therefore, only a very small percentage of cases of multiple myeloma have renal failure as a result of renal amyloidosis. The hyperglobulinemia which is so commonly present in multiple myeloma is probably pathogenetically related to the amyloidosis. Finally there are rare cases in which the kidney is the seat of actual myelomatous deposits (plate 152 E, 331). These infiltrations are focal and may be dismissed as a cause of renal insufficiency. There remains, nonetheless, a lesion directly responsible for renal insufficiency, this lesion has been termed *myeloma nephrosis* and, according to Šikl, was first described by von Decastello in 1909.

### Bence-Jones Protein

The precise nature and source of the Bence-Jones protein or proteose are not clear despite extensive investigations since the time of its

recognition in 1847. The molecular weight of the Bence-Jones protein is about 25,000 to 30,000 as against 68,000 for albumin and 156,000 for globulin. Its molecule therefore is able to pass the glomerular filter, probably without causing injury to the glomerular capillaries or requiring them to be abnormally permeable. It has many properties in common with serum proteins, especially pseudoglobulins, including its solubility in water, its precipitation by 50 per cent ammonium sulfate and its similar refractive index and absorption spectra. The phosphorus content of Bence-Jones protein is low and its content of aromatic amino acids is high (Hewitt). The Bence-Jones protein coagulates at a lower temperature than either albumin or globulin and on further heating is redissolved, to reappear on cooling. An alkaline or strongly acid solution prevents coagulation. It gives a purple biuret reaction unlike the pink of proteoses (Bewley). It has antigenic properties and immune sera can be prepared which differentiate it from other proteins. Bence-Jones protein does not pass through a dialyzing membrane as do albumin and proteoses (Miller and Bactzer). The Bence-Jones proteins from different cases may have variable properties according to Hewitt.

Bence-Jones proteinemia occurs in about 70 to 80 per cent of cases of multiple myeloma and is usually associated with hyperglobulinemia and inconstantly present proteinuria. The evidence points to the myelomatous cells as the source of the protein, and yet there is no correlation between the level of Bence-Jones proteinemia and the amount of tumor present. Bence-Jones proteinemia is said to occur rarely in the absence of myeloma. Boggs and Guthrie long ago reported its presence in a case of carcinoma of the breast with osseous metastases and cited several other reports. Such instances, however, are sufficiently infrequent to make the finding of Bence-Jones proteinemia or proteinuria practically pathognomonic of multiple myeloma. Hyperglobulinemia as high as 15.5 Gm per cent is on record.

### Pathology

#### Gross appearance

The kidneys of myeloma nephrosis are slightly decreased in size, but the surfaces

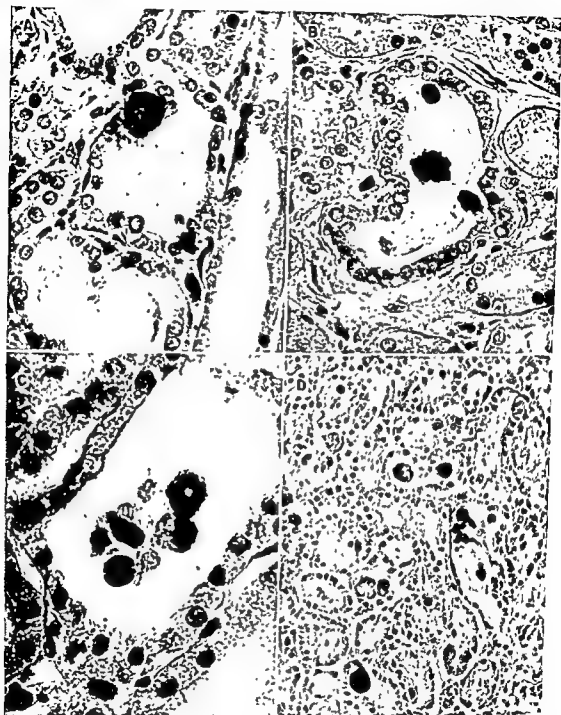


FIG. A. *Sulfathiazole crystal with hyaline cast in distal convoluted tubule*

FIG. B. *Calcified bodies in distal convoluted tubules in lower nephron nephrosis of crush syndrome in a patient without sulfonamides*

FIGS. C AND D. *Greenish-yellow crystals similar to crystals of acetylated sulfadiazine in distal convoluted tubules in yellow fever. These crystals are probably leucine.*

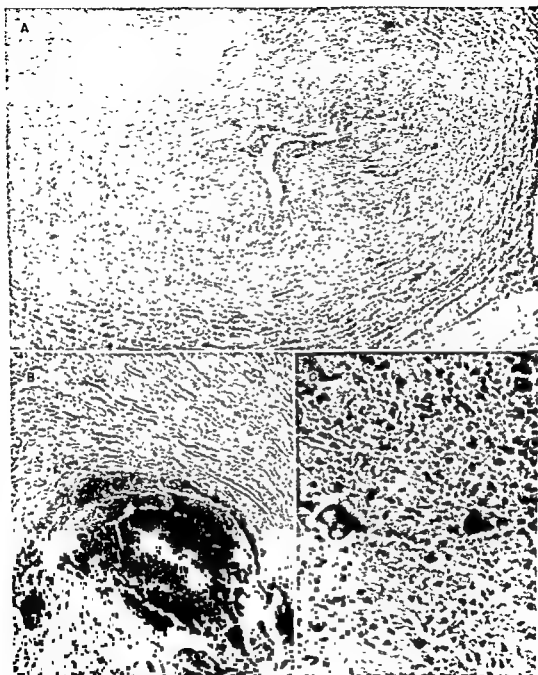


FIG. A. Sulfathiazole urethritis with purulent inflammation about crystals of acetylated sulfathiazole, shown in higher magnification in Figures B and C

FIG. B. Hemorrhagic vulvitis due to sulfathiazole

FIG. C. Crystals of acetylated sulfathiazole in the lumen of obstructing purulent exudate in ureter

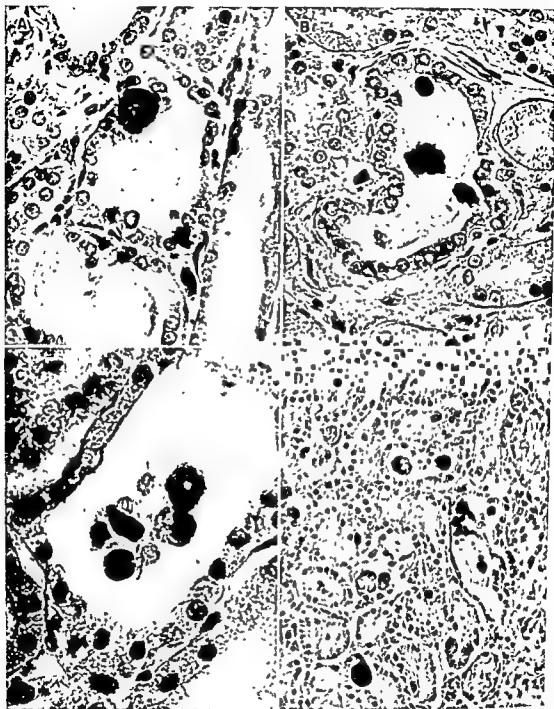


FIG A *Sulfathiazole crystal with hyaline cast in distal convoluted tubule.*

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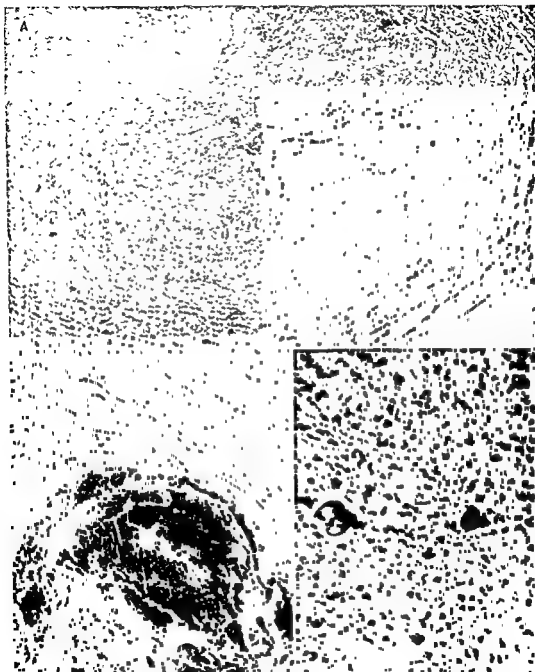


FIG. A Sulfathiazole ureteritis with purulent inflammation about crystals of acetylated sulfathiazole, shown in higher magnification in figures B and C

FIG. B Hemorrhagic calycitis due to sulfathiazole

FIG. C Crystals of acetylated sulfathiazole in midst of obstructing purulent exudate in ureter

tend to be smooth and on sectioning, are pale and wavy (plate 149 A).

### *Histologic appearance*

There are four principal histologic features of myeloma nephrosis: (1) the casts, (2) the tubular epithelial reaction about the casts, (3) the tubular atrophy and (4) the parenchymal nephrocalcinosis ("metastatic calcification").

**Casts:** The casts are localized to the distal portion of the nephron, chiefly to the distal convoluted tubules. They are uncommonly in the limbs and loops of Henle. They are brightly acidophilic, dense, and occasionally in concentric rings of variable thickness (plate 149 B, C). The central portions of the casts tend to be fragmented, granular, pocked with small locules and unevenly calcified. Distorted, desquamated epithelial cells and a few leukocytes may be included. More often the casts are not lamellated but are composed of a similar dense material staining irregularly pink with eosin but artefactually broken apart into several segments in the manner of glomerular amyloid. The casts do not take the metachromatic stains for amyloid.

**Crystals:** In rare instances, crystals are found in the tubules, usually in the distal convoluted tubules, free or in association with the casts, and infrequently in the loops and limbs of Henle. These crystals are short and long, needle shaped, hexagonal, prismatic, rhomboid and arranged singly or in packets (plate 152). They are not birefringent and as a rule are stained with the acidophilic dyes although some do not take the stain. According to Šíkl, this observation was first reported verbally by Lohlein in 1913 and published by him eight years later. Fourteen cases have been reported to date (Šíkl), no such finding was noted in 18 of our

own cases. Professor Šíkl was kind enough to let us have some of his material for study. No special stains are required for the demonstration of these crystals. In 6 of the reported cases, Bence-Jones proteinuria was present; 2 are regarded as negative and in the remaining 6, the information is not available. In 5 of these latter cases, the bone marrow was not examined or details are altogether lacking, a sixth case was reported as a leukemic lymphadenosis. Those cases with Bence-Jones proteinuria and renal crystals were in cases of plasmocytic myeloma.

The crystals are stated to resemble the Bence-Jones protein that has been crystallized *in vitro* although they are not dissimilar in shape to the crystals of hemoglobin (plate 126 D). By their distribution and morphology, the crystals seem not to have been deposited in the casts but to have risen from them. They are present also in the renal epithelium of proximal convoluted tubules, an observation first made by Apitz (plate 152 D). Some of the crystals closely resemble the plasmocellular crystalline inclusions (Russell bodies) so prominent in the infiltrate of rhinocleroma. Similar crystals have been observed in the cytoplasm of myelomatous plasma cells (Glaus) and in other organs than the kidney (Šíkl, Neumann).

**Tubular epithelial reaction:** One of the almost specific identifying features of the myeloma kidney is the syncytium of epithelial cells about the dense casts. These collections of cells are commonly referred to as foreign body giant cells provoked by the irritative casts. However, detailed studies of the transitional phases in their formation suggest that they represent a fusion of the tubular epithelium about the casts. These syncytia are always intraluminal. Usually, the adjacent single tubular cells are

FIG. A Von Gierke's disease. Kidney from a ten week old infant with von Gierke's disease. The glycogen is seen as fine black granules in the distal convoluted tubules, in the wall of an arteriole, and in the cells of the glomerulus. The proximal convoluted tubules did not contain glycogen in this case (Best's carmine stain). Contrast these fine vacuoles with the large vacuoles of glycogen in diabetes mellitus (plate 108). (Histologic slide obtained through courtesy of Dr. M. Wachstein.)

FIG. B Alkaline phosphatase in the kidney of von Gierke's disease illustrated in figure A. There is no abnormality of distribution of either alkaline or acid phosphatase.

FIG. C Heart in von Gierke's disease. The vacuoles within the myocardial fibers contain glycogen. From case illustrated in figure A.



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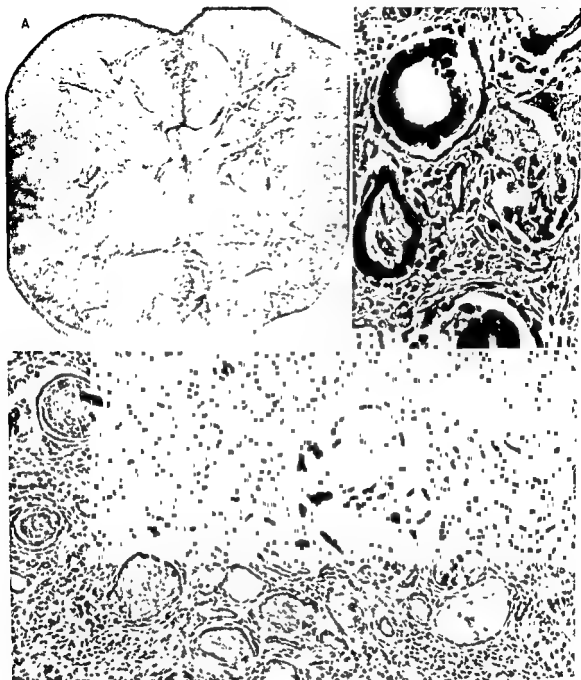


FIG A Kidney from multiple myeloma showing no distinctive gross features except, perhaps, for firm waxy appearance

FIG B Dense laminated casts with soft cores in a case of multiple myeloma with Bence-Jones proteinuria

PLATE 150. NEPHROSIS OF DISTAL NEPHRON: MULTIPLE MYELOMA



FIG. A Kidney of multiple myeloma with Bence-Jones proteinuria showing minimal involvement in the form of dense casts with associated alteration of epithelial cells and slight interstitial fibrosis.

FIG. B Centrally softened cast of multiple myeloma with peripheral ancytosis of tubular epithelial cells in a case with Bence-Jones proteinuria.

FIG. D Centrally calcified casts of kidney in a case of multiple myeloma.

FIG. C Renal metastatic calcification of specific variety, in a case of extensive myeloma.

FIG. E Metastatic calcification in a char cast of myeloma kidney showing giant cells of tubular epithelium.

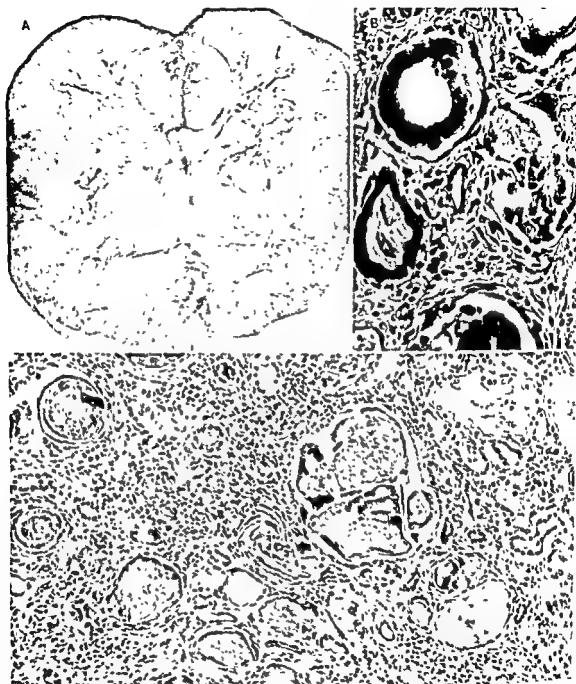


FIG A Kidney from multiple myeloma showing no distinctive gross features except, perhaps, for firm waxy appearance

FIG B Dense laminated casts with soft cores in case of multiple myeloma with Bence-Jones proteinuria

FIG C High power view of multiple myeloma showing dense infiltrate of plasma cells with eccentric nuclei and prominent nucleoli



FIG. A Kidney of multiple myeloma with Bence-Jones proteinuria showing minimal involvement in the form of dense casts with associated alteration of epithelial cells and slight interstitial fibrosis

FIG. B Centrally softened cast of multiple myeloma with peripheral syncytium of tubular epithelial cells in a case with Bence Jones proteinuria

FIG. D Centrally calcified casts of kidney in a case of multiple myeloma

FIG. C Renal metastatic calcification of a non-specific variety, in a case of extensive myelomatosis

FIG. E Metastatic calcification in a characteristic cast of myeloma kidney showing giant cells made up of tubular epithelium

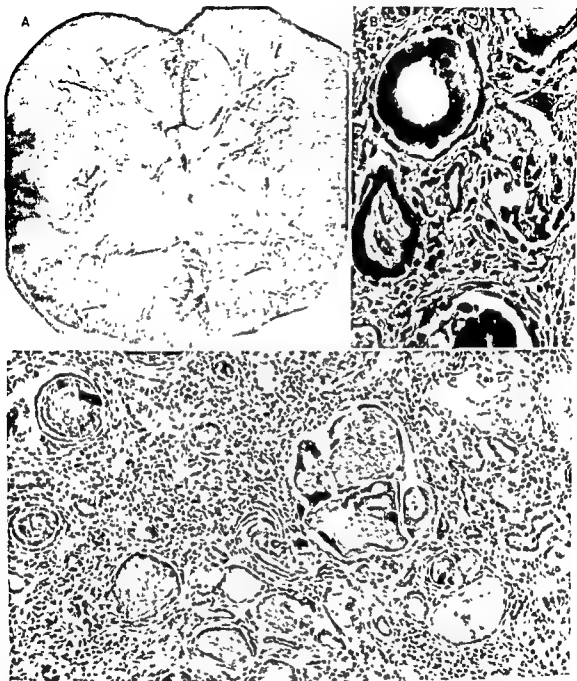


FIG A Kidney from multiple myeloma showing no distinctive gross features except, perhaps, for a waxy appearance

FIG B Dense laminated casts with soft cores in a case of multiple myeloma with Bence-Jones proteinuria

FIG C Characteristic picture of kidney in multiple myeloma showing laminated casts with granular soft centers and giant cells in various stages of development. These giant cells appear to be actually a syncytium of tubular epithelial cells rather than foreign body giant cells.



FIG A Kidney of multiple myeloma with Bence-Jones proteinuria showing minimal involvement in the form of dense casts with associated alteration of epithelial cells and slight interstitial fibrosis

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FIG D Centrally calcified casts of kidney in a case of multiple myeloma

FIG C Renal metastatic calcification of a non specific variety, in a case of extensive myelomatosis

FIG E Metastatic calcification in a characteristic cast of myeloma kidney showing giant cells made up of tubular epithelium

of similar quality and show degenerative as well as regenerative features. The epithelial cells of the proximal portions of the involved tubules may also show degenerative and regenerative changes in the absence of casts. In this connection, it should be mentioned again that syncytial masses of fused epithelial cells are found commonly in normal kidneys of patients over 40 years of age (plate 151 C). These should not be confused with the epithelial syncytium about casts in myeloma kidneys. Giant cells form also about calcific deposits (plate 151 D), and about foreign bodies, for example, sulfonamide crystals (plate 151 B), and of course as parts of various tubercles. These should offer no diagnostic difficulty.

**Tubular atrophy** The tubular atrophy in myeloma nephrosis has been attributed by some observers (Perla and Hutner) to the effects of arteriosclerosis, but there can be no doubt that tubular atrophy occurs also on another, more specific basis. The frequent disparity between the marked degree of tubular atrophy and the relatively early stages of arteriosclerosis by itself suggests the incomplete dependence. In cases in which the vascular sclerosis is appreciable, corresponding tubular change may naturally be expected, and usually the degree of correlation can be made with reasonable accuracy. However, the bulk of the tubular atrophy of the myeloma kidney is independent of vascular sclerosis and is constantly associated with dense obstructive casts. There is also moderate interstitial fibrosis with slight inflammatory infiltrate. Despite extensive tubular change, the appertaining glomeruli may in some cases show a complete absence of sclerotic atrophy, such atrophy would be expected if the pathogenesis were on the basis of vascular sclerosis (plate 149 C). The glomeruli in these instances are free of the fibrotic change usually associated with hydronephrotic atrophy except for mild to moderate thickening of Bowman's capsule. It is of additional concern that the tubular atrophy attributed to the proteid casts does not cause dilatation of tubular lumens and Bowman's spaces proximally, but, instead, the lumens are contracted. Plugging of tubules obviously may cause hydronephrotic atrophy, just

as complete obstruction of the ureter may under certain circumstances cause renal atrophy without pelvic dilatation.

**Parenchymal nephrocalcinosis** ("metastatic" calcification): Parenchymal nephrocalcinosis ("metastatic" calcification) is a common finding in the kidneys of patients with multiple myeloma. The location of calcific deposits in metastatic calcification happens to be the same as that chiefly involved in the other tubular changes of myeloma nephrosis. Hence, it is not surprising that the casts and the tubular epithelium about the casts may be calcified. However, the possibility that the proteid casts of myeloma have an added affinity for calcium cannot be altogether excluded, especially in view of the focal granules of calcium observed in their centers, in the absence of tubular epithelial calcification. The metastatic calcification is a consequence principally of the lytic myelomatous lesions of bone, although often no direct correlation obtains between the extent of the osseous lesions and the renal calcification. The renal insufficiency may contribute to the calcification by its effects on the parathyroid glands and the resultant secondary hyperparathyroidism.

**Glomeruli** No specific glomerular changes occur in cases of multiple myeloma. There is often found a low-grade diffuse thickening of glomerular capillaries but this is quite non-specific and is of the type seen, for example, in atrophic kidneys of chronic pyelonephritis or hydronephrosis. In 1935, Fould observed what were considered inspissated plugs of protein in the glomerular capillaries in a case of multiple myeloma. The renal insufficiency in this case was attributed to glomerular obstruction by the capillary plugs, the formation of which was believed to be related to the hyperproteinemia. Data on the level of the proteinemia, however, are not given and studies of the urine for Bence-Jones protein were not done. The description of the glomerular lesions is reminiscent of those seen occasionally in shock and dehydration and illustrated in plates 255 and 256. Actually, the patient just referred to did have a hemorrhagic diathesis with a marked anemia, and required transfusions. This lesion, in our

PLATE 151. NEPHROSIS OF DISTAL NEPHRON: MULTIPLE MYELOMA (DIFFERENTIAL DIAGNOSIS OF CASTS)



FIG. A Insipiated casts and syncytia of tubular epithelial cells in a case of chronic glomerulonephritis in a 6 year old. This preense formation is rare outside of cases of myeloma.

FIG. B Giant cells provoked by crystals of acetylated sulfathiazole.

FIG. C Syncytial proximal tubular epithelium common as a finding after the fourth decade.

FIG. D Reactive giant cell to a calcium cast in a case of nephrocalcinosis secondary to osseous metastases. This reaction is unusual in this condition.



experience, is a terminal phenomenon and should be dissociated from the specific lesions of multiple myeloma

### Summary

In summary, for all practical purposes, the specific diagnosis of multiple myeloma may be made with considerable assurance on the basis of a properly weighed integration of the type of histologic changes herein described. It is plain that these changes may occur in the absence of renal insufficiency when they are not widespread, when they are extensive, they lead to progressive renal insufficiency and even to anuria (Holman). They are the preponderant cause of renal dysfunction in patients with multiple myeloma.

The correlation of myeloma nephrosis with Bence-Jones proteinuria is probably much greater than the published reports indicate. Undoubtedly the reason concerns the technical inadequacy of the performance of the tests for Bence-Jones proteinuria, the use of urine that has been at room temperature, or the insufficient number of determinations made, in view of the known intermittency of Bence-Jones proteinuria. The many pitfalls are detailed in the report by Jacobson and Wilner. There does not seem to be a correlation between the total level of blood proteins or the degree of proteinuria in multiple myeloma, and the extent or incidence of myeloma nephrosis or renal dysfunction, nor is the renal lesion of myeloma nephrosis found in other diseases with hyperglobulinemia, such as kala-azar, Boeck's sarcoid and disseminated lupus erythematosus. Experimentally, there is a sharp discrepancy in the reports as to the histologic effects on the kidney of the administration of Bence-Jones protein to normal animals, McMahan and Magnus-Levy describe prominent tubular changes as opposed to the essentially negative findings of Forbus, Perlzweig and Parfentjev.

The study of renal function in patients with myeloma, by the use of clearance tests, yielded altogether unsatisfactory results (Armstrong).

### Gout

#### Introduction

There exists considerable confusion regarding the renal pathology of gout. The "gout kidney" is commonly spoken of, but, to different people, it may connote glomerulonephritis, arteriosclerosis, interstitial nephritis, a kidney with multiple small cysts, urate deposits in various locations, pyelonephritis, or combinations of these lesions. Actually, there is a specific lesion in gout, but it appears not to be the one generally in mind when the "gout kidney" is mentioned.

#### Pathology

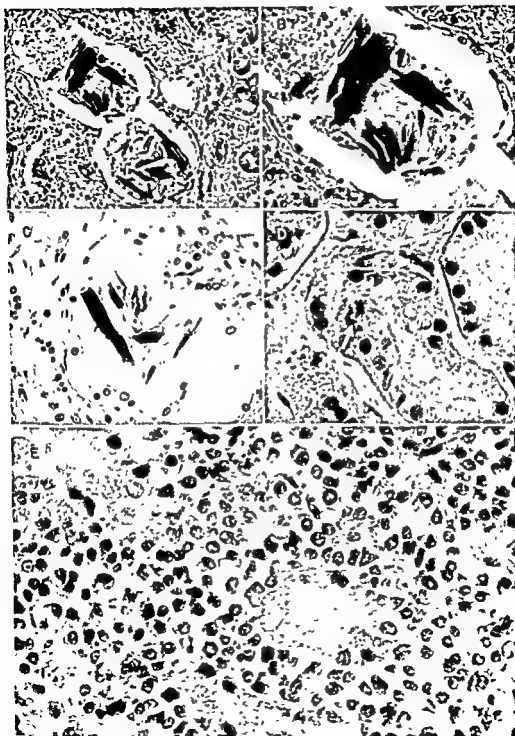
The lesion of gout is made specific by the presence of sodium acid urate crystals primarily in the lumens of the collecting tubules, but with extension into the interstitial tissue, particularly of the lower portions of the pyramids. The tubular epithelium about the casts of the crystals may be entirely destroyed (plates 153, 154 A) and their localization thereby missed. These crystals which are found in the great majority of cases of gout, are easily recognized by their long, slender shape (or by the shape of the mold from which they have been dissolved in paraffin sections), by their disposition in sheaves, by their radial arrangement, and by the foreign body giant cells about their periphery in association with relatively little lymphocytic or histiocytic reaction. The crystals of gout differ in appearance from those of the "uric acid infarcts" of children, which are presumed to be ammonium rather than sodium urate. The urate crystals isolated from tophi are birefringent, but the crystals originally birefringent, are usually dissolved in paraffin sections of the kidney. Some of the

FIGS. A, B AND C Crystals of Bence-Jones protein within tubules, from a case of multiple myeloma. (Histologic slide obtained through the courtesy of Prof. H. Sisk of Prague.)

FIG. D Crystals of Bence-Jones protein within epithelial cells of proximal convoluted tubules (arrow).

FIG. E Myelomatous (or myelosarcomatous) growth within renal parenchyma from a case of multiple myeloma, plasma cell type.

PLATE 152. NEPHROSIS OF DISTAL NEPHRON: MULTIPLE MYELOMA



(Legends on facing page)

experience, is a terminal phenomenon and should be dissociated from the specific lesions of multiple myeloma

### Summary

In summary, for all practical purposes, the specific diagnosis of multiple myeloma may be made with considerable assurance on the basis of a properly weighed integration of the type of histologic changes herein described. It is plain that these changes may occur in the absence of renal insufficiency when they are not widespread, when they are extensive, they lead to progressive renal insufficiency and even to anuria (Holman). They are the preponderant cause of renal dysfunction in patients with multiple myeloma.

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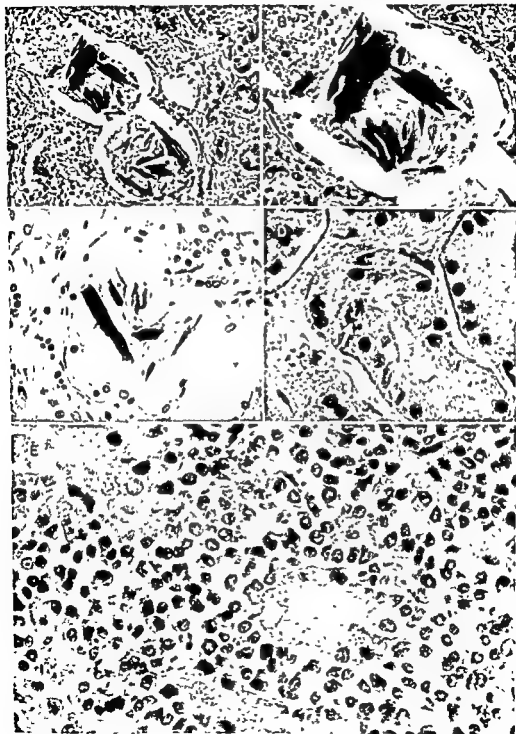
#### Pathology

The lesion of gout is made specific by the presence of sodium acid urate crystals primarily in the lumens of the collecting tubules, but with extension into the interstitial tissue, particularly of the lower portions of the pyramids. The tubular epithelium about the casts of the crystals may be entirely destroyed (plates 153, 154 A) and their localization thereby missed. These crystals which are found in the great majority of cases of gout, are easily recognized by their long, slender shape (or by the shape of the mold from which they have been dissolved in paraffin sections), by their disposition in sheaves, by their radial arrangement, and by the foreign body giant cells about their periphery in association with relatively little lymphocyte or histiocytic reaction. The crystals of gout differ in appearance from those of the "uric acid infarcts" of children, which are presumed to be ammonium rather than sodium urate. The urate crystals isolated from tophi are birefringent, but the crystals originally birefringent, are usually dissolved in paraffin sections of the kidney. Some of the

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FIG. D Crystals of Bence-Jones protein within epithelial cells of proximal convoluted tubules (arrow)

FIG. E Myelomatous (or myelosarcomatous) growth within renal parenchyma from a case of multiple myeloma, plasma cell type



(Legends on facing page)

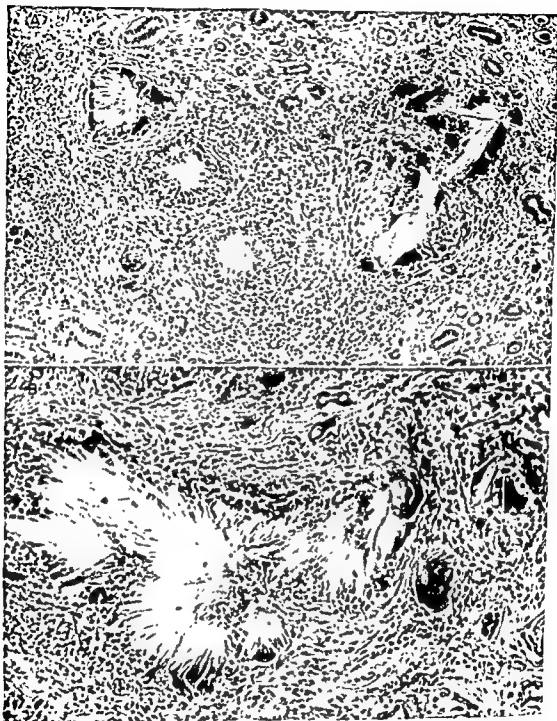


FIG. A. *Nephrosis of gout with foci of sodium acid urate crystals and giant cells within the col-*  
*lapsed tubules. The crystals are not seen under*  
*ordinary light, but are readily*  
*dissolved in the preparation of paraffin sections*

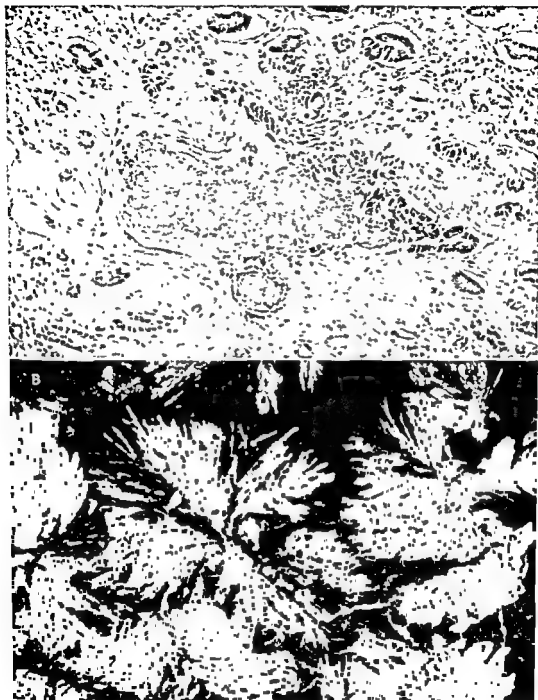


FIG. A. Gout. A cast of sodium acid urate crystals in a collecting tubule in which portions of the lining epithelium are still present

FIG. B. Gout. Birefringent sodium acid urate crystals

PLATE 153. URIC ACID "INFARCTS"

A

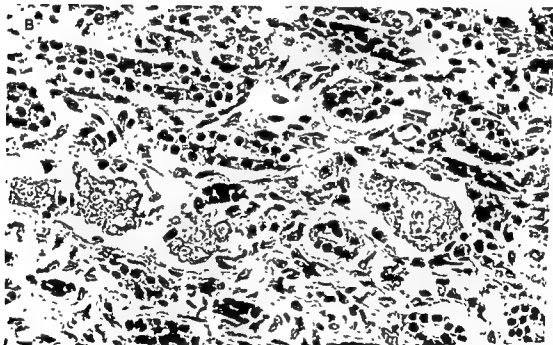
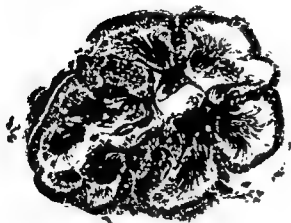


FIG. A *Uric acid "infarcts" in the kidney of a newborn infant. The uric acid is present in the light colored streaked portions of the pyramids*

FIG. B *Isotropic uric acid crystals in lumens of collecting tubules. Similar crystals may be seen occasionally in treated cases of leukemia. Ammonium urate is said also to be present*

crystals may become ground into an amorphous urate dust (plate 154 A).

Such crystalline deposits are rarely responsible for renal insufficiency. The renal damage that is commonly present in kidneys of gouty patients are those judged to be incidental to the obesity, hypertension and age which characterize such patients. Of 55 patients with gout (average age 52 years), 17 had renal insufficiency (Schnitzer and Richter). In other words, the resulting increased but nonspecific tendency to develop arterial and arteriolar nephrosclerosis would seem to be responsible for much of the renal damage erroneously attributed directly to gout. In this connection it is of interest to note Aldis' view that gout should be suspected in patients with "long continued uremia of years' duration." He finds that these patients are all males without the usual signs of gout and generally are younger than those with classical gout. He refers to the condition in these patients as "secondary gout," attributing the rise in uric acid level in the blood not to faulty purine metabolism but to the consequence of inadequate amounts of effectively functioning renal tissue.

Although the chief intent of this section is to emphasize that the basis for the renal dysfunction in patients with gout is not the specific effect of the abnormal metabolism of uric acid, it would be incorrect to conclude that deposits in the kidney are never detrimental. The masses of urate crystals collect in the apices of the pyramids (plates 153, 154 A) which are critical bottlenecks in the urinary outflow. If a sufficient number of the ducts of Bellini are obstructed, renal function is compromised just as it occasionally is when calcium deposits occlude the outflow at this same site. Fortunately, such extensive blockage is rare. In isolated instances, however, the stasis produced in the collecting tubules clogged by urate crystals may lead to a superimposed localization of pyogenic organisms with the subsequent development of acute pyelonephritis (Brown and Mallory). The acute pyelonephritis may

lead to immediate renal failure, or repeated attitudinal episodes of acute pyelonephritis may occur in these kidneys made vulnerable by the obstructive packets of crystals until finally insufficient renal tissue remains. In most instances of renal failure in patients with gout, the specific, obstructive, pyelonephritic element caused by the urates is merely one of several factors in the renal embarrassment, associated vascular disease of the kidney is one of the major accessory components.

#### URIC ACID "INFARCTS"

The term uric acid "infarcts" is really a loose designation referring to the golden yellow, fairly sharply defined wedge located in the papillae of the renal medulla (plate 155 A). These lesions are not actually infarcts but merely the focal collections of uric acid crystals in the terminal collecting tubules (plate 155 B). Such masses of crystals appear to occur when rapid destruction of nuclei takes place as in leukemia, in occasional infections, or, normally, in the newborn. It has been stated that in the latter physiologic state, there is an inadequate supply of the enzyme uricase available for the need of the immediate postnatal period. No renal dysfunction has been attributed to the uric acid infarcts.

The collecting tubules occupying the apex of the pyramids are filled with spherical, sharply rimmed, laminated, acidophilic masses of uric acid crystals. The crystals are about 10 to 20 microns in diameter and are not birefringent, unlike those of gout. These crystals, along with granular protein precipitate and desquamated tubular epithelium, form casts. From the manner of denudation of the collecting tubules, it appears that they are the source of the epithelial cells within the uric acid casts. Evidence of nuclear reaction in the form of irregularity and hyperchromatism in these epithelial cells indicates that the casts are irritative. No significant dilatation is present in the portions of the nephron proximal to the casts nor is there any interstitial inflammation.

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# 8. Interstitial Nephritis

## ACUTE DIFFUSE INTERSTITIAL NEPHRITIS

### Introduction

Acute diffuse interstitial nephritis complicates bacterial, rickettsial, and viral infections, as well as the administration of sulfonamides, and possibly other chemicals. More specifically, this form of nephritis has followed diphtheria, scarlet fever, Ludwig's angina, erysipelas, typhoid fever, infected wounds, typhus fevers, smallpox, measles, and other diseases. The clinical manifestations are likely to occur earlier in the course of the disease, often during the first week, for example, than does the acute diffuse glomerulonephritis after scarlet fever. Acute diffuse interstitial nephritis is rarely diagnosed clinically although it would seem that the early onset of moderate to severe oliguria, or, rarely, anuria, with azotemia without other apparent cause, might lead to the suspicion of acute interstitial nephritis, especially in infectious diseases. Hypertension and edema are not present, albuminuria is slight or absent, hematuria and slight pyuria occur occasionally.

### Pathology

#### Gross appearance

The kidneys are soft and enlarged from one and a half to twice normal size. The capsules are easily stripped from a smooth, mottled, purple-red, yellowish-brown, often finely hemorrhagic surface. The sectioned surface is moist, and is characterized by a thickened cortex, discolored with linear streaks of cellular infiltrate in contrast to the deep red of the adjacent hyperemic vessels. The medulla is deeply congested.

#### Histologic appearance

The histologic picture of acute interstitial nephritis varies in the quality of the cells constituting the infiltrate. In all cases, however, it would seem best to adopt the requirement that the diagnosis of acute interstitial nephritis be based on the actual finding of infiltrate

diffusely throughout the kidney, and, above all, within the cortical interstitium.

The infiltrate is composed predominantly either of plasma cells, or of eosinophilic leukocytes (plates 156 A, 157). In some instances, the infiltrate is made up of a mixture of plasma cells, eosinophilic leukocytes, and scattered polymorphonuclear leukocytes and histiocytes. Occasionally the inflammatory cells undergo karyorrhexis. The amount of interstitial edema is variable, a separate designation of "serous" interstitial nephritis does not appear justified. Focal hemorrhages may be present. There is no distinction between the infiltrate provoked by products of bacteria and that produced by the sulfonamides.

The glomeruli are not histologically altered. The tubules appear intact except for frequent foci of hyaline granular degeneration of the epithelium of the proximal convoluted tubules. Small clusters of purulent exudate are scattered in the distal tubules, even when the interstitial infiltrate is almost exclusively plasmocellular (plate 157 C). The vessels generally are not remarkable although, occasionally, focal thrombophlebitis and an acute fibrinoid smudgy degeneration of an isolated arteriole may be noted. The peritubular capillaries are often filled with mononuclear cells that are not representative of the peripheral blood and appear to be the source of the interstitial infiltrate (plate 170 A).

Undoubtedly less severe degrees of acute diffuse interstitial nephritis remain undiagnosed and are survived. It is likely that restitution in such cases takes place, not by scarring but by complete resolution. The terms chronic interstitial nephritis or chronic parenchymatous nephritis have become obsolete and should not be regarded as the chronic stage of acute interstitial nephritis.

The acute diffuse interstitial nephritis is probably invariably fatal. It still remains unclear precisely how the renal shutdown is produced by the interstitial infiltrate. The ob-





FIG A *Acute interstitial nephritis* following scarlet fever. The infiltrate consists chiefly of lymphocytes and plasma cells with a scattering of polymorphonuclear leukocytes. The tubules are preserved although some contain exudate.

FIG B *Lymphosarcoma* of kidney in which interstitial neoplastic cells superficially simulate acute interstitial nephritis.

FIG C *Leukemia* of kidney which, in this interstitial form, also simulates acute interstitial nephritis.

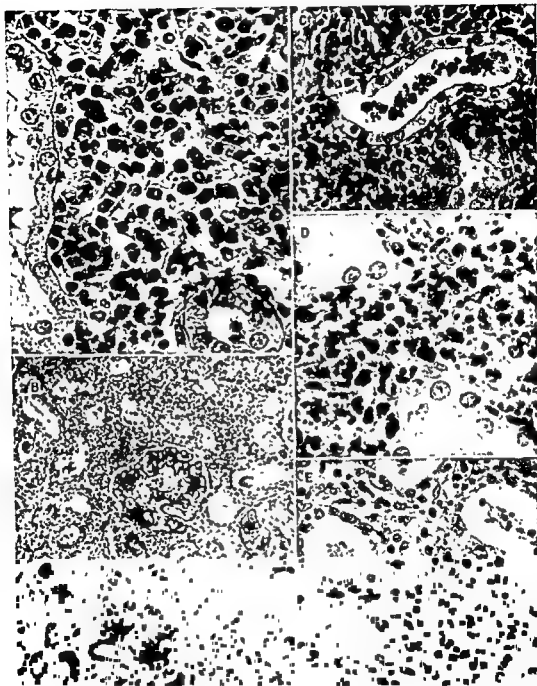


FIG. A. Infiltrate of plasma cells and lymphocytes

many plasma cells and lymphocytes

FIG. B. Acute interstitial nephritis superimposed on amyloidosis of the kidney

FIG. C. Exudate in distal convoluted tubule in acute interstitial nephritis

FIG. D. Necrobiotic distortion of polynuclear cells in interstitium in acute interstitial nephritis

FIG. E. Interstitial edema in acute interstitial nephritis

vious presumption is that the infiltrate increases intrarenal pressure with compression of vessels. The pressure is apparently not relieved by decapsulation. Moreover, an even more compact and extensive interstitial infiltrate occurs relatively frequently in the various lymphoblastomas and leukemias without renal dysfunction (plate 319 C). Possibly the difference is dependent on the rapidity with which the infiltrate is deposited.

### *Pathogenesis*

Fishberg's suggestion that "acute interstitial nephritis is due to invasion of the kidneys by organisms rather than to the action of the toxic products as in glomerulonephritis" is not the most credible interpretation of the pathogenesis of this disease. Positive cultures of the kidneys in the presence particularly of sepsis but also of postmortem invasion of bacteria must obviously be given little weight. The finding of culpable bacteria within inflammatory foci of paraffin sections of kidneys with acute diffuse interstitial nephritis is extremely uncommon and would certainly not seem to merit *direct* causal association. The more plausible concept is that the diffuse interstitial inflammation is the reaction either to toxic products of bacteria, rickettsias, or viruses, or their allergens.

In view of the occurrence of acute interstitial nephritis as a reaction to sulfonamides, the role of allergens with various haptens is stressed. To dismiss the possibility of allergy or altered local tissue reactivity in the pathogenesis of a lesion in humans because of the time relationship to the initial infection is unwarranted. Furthermore, to suggest that when the glomeruli are involved in an acute glomerulonephritis, the pathogenesis must be different

from that concerned with inflammation of the interstitium merely because the two structures are so completely different, is to overlook a basic feature of the target of allergens. In other words, some patients with allergy will react with asthma, others with similar allergies will develop a skin rash, and still others will manifest their allergy with an acute peritoneal reaction, or intestinal upset. Similarly, glomeruli may be the target in one case, the interstitium in another, the vessels in the third. Moreover, it is becoming increasingly clear that neither eosinophilic leukocytic inflammation, nor fibrinoid degeneration constitute the only response to allergy. Plasma cells, various histiocytes, and lymphocytes (Allen and Spitz) are also concerned, often to the exclusion of eosinophilic leukocytes.

### ACUTE FOCAL INTERSTITIAL NEPHRITIS

The acute focal interstitial nephritis is to be distinguished histologically from acute diffuse interstitial nephritis. The failure to establish this distinction has been responsible for some confusion in the literature. Acute focal interstitial nephritis may occur in association with any sepsis, including Weil's disease (plate 166 A), as a reaction to a variety of drugs and poisons, and in hemoglobinuric and cholemic nephrosis, and possibly in syphilis. This focal interstitial reaction in the kidney may be indistinguishable from that of infectious mononucleosis. Rarely is the focal infiltration so extensive as to be solely responsible for the degree of renal insufficiency that occurs in the diffuse disease. In the focal disease, the infiltrate tends to localize at the corticomedullary junction or even exclusively in the medulla (plate 171 A).

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## 9. Specific Infections

### TUBERCULOSIS

#### *Introduction*

PERHAPS one of the most satisfactory viewpoints of the pathogenesis of organ tuberculosis is embodied in Ranke's classification of tuberculosis (Jaffé). According to this classification, four stages in the evolution of tuberculous infection occur:

- 1 The stage of the primary complex
- 2 The stage of early generalization
- 3 The stage of localization
4. The stage of late generalization

The primary (Ghon) complex (parenchymal infection plus the lymph node component) occurs principally in the lung, but may occur at a variety of other sites including the intestine or even the penis after circumcision. The establishment of the primary complex, which tends to become calcified, is followed in the next few years by the stage of early generalization. This stage takes place usually in childhood and is generally overlooked clinically because of the mildness of the symptoms. As a result of this early dissemination, the tubercle bacilli may persist in a dormant state for years in one or more organs. A healed lesion of this sort is illustrated in plate 162 B. These organisms are activated in later life when "resistance" is lowered for one of a variety of reasons (for example, undernourishment, debilitating diseases, or diabetes mellitus). Fatal miliary dissemination or the final stage of "late generalization" may then result from the isolated organ tuberculosis thus produced.

There has been criticism of this concept of tuberculosis as there has been of most. An alternate concept is that the tubercle bacilli do not lie latent in the kidney—or other organ in question—but reach it by the hematogenous seeding of organisms from an activated focus usually in the form of an apical or subapical (Aschoff-Puhl or Simon) lesion. In either in-

stance the renal localization is from a hematogenous dissemination of bacilli. The renal localization through lymphatic spread or by direct ascension from the lower urogenital tract probably accounts for a very small fraction of cases of renal tuberculosis unlike the suppurative pyelonephritis secondary to cystitis and ureteritis caused by pyogenic organisms.

#### *Miliary Renal Tuberculosis*

Miliary renal tuberculosis follows a hematogenous dissemination of tubercle bacilli (Ranke, stage IV) from an activated focus in the kidney itself or some other organ. Renal miliary tuberculosis is therefore a part of a generalized miliary tuberculosis, obviously, in most cases of death due to miliary tuberculosis, the kidneys are involved. This overwhelming form of tuberculosis is rarely recognized clinically because it occurs so soon before death and does not lead to significant renal dysfunction. The latent dissemination of early tuberculosis (Ranke, stage II) may lead to a few miliary renal tubercles which subsequently heal completely or, as stated, act as a latent focus for future activation (plate 162 B).

The miliary tubercles, unlike the lesions of clinical renal tuberculosis, are localized largely to the cortex, however, they may also involve the medulla (plate 160 B). Rarely, a histologic picture superficially resembling focal endocarditic glomerulonephritis is noted.

#### *Ultero-caseous Renal Tuberculosis*

The lesions that result in chronic destructive renal tuberculosis select the pyramid—usually at its apex rather than its base—for the site of initial localization (plate 160 A). It is interesting that the organs such as the liver and spleen which are heavily seeded with tubercles in miliary tuberculosis are rarely involved by extensive ultero-caseous tuberculosis, in contrast to the kidneys (Rich). The mere contact of tissues with numbers of bacilli is

not the answer to this disparity. The involvement is usually unilateral for a while but, sooner or later, the opposite organ is affected. The explanation of the tendency for bilateral involvement of paired organs is also incomplete. For example, if the left kidney is tuberculous, why does not the left adrenal become involved before the right kidney? Common connecting channels can not be the entire explanation in view of the situation applying to the adrenals as well (Rich).

The tuberculous focus of the pyramids tends to begin at either pole of one kidney and to spread by ulceration and cavitation outward to the entire pyramid and cortex and inward to involve the pelvic mucosa. The caseation may simulate grossly the lesions of necrotizing papillitis (plate 161 C). With ulceration through the papilla, the process spreads to other papillae, to the mucosa of the entire pelvis and to the ureter. The progressive caseous destruction and cavitation may lead to a bosselated enlargement of the kidney to  $1\frac{1}{2}$  to 2 times the normal size. The sectioned surface of such an organ with tuberculous pyonephrosis shows it to be hydronephrotic with cavities lined by ragged granular cavities with caseous yellow walls in place of the pyramids, yellowish grey streaks and nodules in the adjacent cortex, and ulceration and thickening of the pelvis (plate 161 A).

The stage of the lesion may vary from one part of the kidney to another. Irregular areas of fibrosis and calcification may occur. The perirenal fat and capsule may become markedly scarred and adherent to the kidney and other structures. The pelvic infection may extend to the ureter causing ulcerative thickening of its wall and stricture of its lumen with consequent aggravation of the hydronephrosis. There appears to be no positive correlation between the extent of the involvement of the kidney on the one hand, and the ureter on the other. Actually the lesion referred to as the "closed" or "putty" kidney is one characterized by complete pultaceous destruction of the kidney without ureteral involvement. This process is sometimes called "autonephrectomy" and occurs in

about 10 per cent of cases of tuberculous pyonephrosis and, with an adequate opposite kidney, may be survived by the patient for many years.

Renal tuberculosis is often masked clinically because the symptoms are often interpreted as primarily due to the bladder. Frequency of urination, both day and night, dull local pain, dysuria, dribbling, microscopic hematuria (gross hematuria is rare) and "sterile" pyuria (with ordinary stains) are the common symptoms. There may be a remarkable lack of constitutional symptoms despite apparently extensive renal involvement.

#### *Toxic Tuberculous Nephritis*

"Toxic nephritis" caused by tuberculosis is mentioned in text books as one of the varieties of renal tuberculosis. Apart from the gamut of changes that may occur within a tubercle, we have no personal information as to precisely what this term means, nor is it defined histologically in the texts. It is well known that diffuse glomerulonephritis is a rare complication of pulmonary tuberculosis (15 cases in 2800 patients, Holten) and even when it does occur in such cases, secondary invaders might have been the responsible agents.

#### RENAL SARCOIDOSIS

Sarcoidosis of the kidney is a rare histologic finding. Sarcoidosis has been reported as being responsible for renal insufficiency (Klinefelter and Salley), but histologic documentation is lacking. In those cases that were examined pathologically, only infrequent and isolated foci of sarcoidosis were found as in the case illustrated in plate 163. Spencer and Warren in 1938 stated that theirs was the first report of renal sarcoidosis. Longcope in 1941 observed the renal lesions in 3 of 4 autopsied cases of sarcoidosis. The sarcoid tubercles in the kidney are quite like those in other organs, consisting of "hard," epithelioid, noncaseating tubercles with giant cells and even Schaumann bodies (plate 163 B). No asteroid bodies were found in the few tubercles seen in our case, nor are they mentioned in the reports of others on the renal lesions. Renal calculi may be associated

with generalized sarcoidosis (Albright and Reinfenstein).

### SYPHILITIC LESIONS OF THE KIDNEY

The following lesions of the kidney have been attributed to syphilis.

- 1 Congenital interstitial nephritis
- 2 Gumma
- 3 "Nephrosis"
4. Focal interstitial nephritis (Rich)
5. Hemosiderosis and hemoglobinuric nephrosis (rarely) secondary to paroxysmal cold hemoglobinuria

#### 1 Congenital interstitial nephritis

The kidney of congenital syphilis is characterized by interstitial inflammation in association with great numbers of treponemas in the interstitium, in the tubular lumens, and among the tubular epithelial cells.

#### 2 Gumma

The syphilitic gumma of the kidney is now rarely seen. The histologic picture is that of a gumma in other organs. Some observers have regarded multiple irregular scars in the kidneys of syphilitic individuals as healed gummas, principally on the basis of exclusion of other diseases. For all practical purposes, the renal gumma is an obsolete lesion.

#### 3 Syphilitic "nephrosis"

There is said to be a third form of renal involvement in syphilis which is manifested clinically by the sudden onset of the nephrotic syndrome without renal insufficiency, usually in the secondary stage, and which is stated to clear promptly with antiluetic therapy (Heyman and Brown). Some cases, nonetheless, do not respond to antiluetic or any other type of therapy (Fishberg). The histologic proof of the existence of such a specific lesion is not complete. However, the dramatic clinical response to antiluetic treatment makes it highly probable that syphilis is etiologically concerned. Until adequate histologic evidence is presented, it might be provisionally assumed that there develops a remarkably acute, increased glomerular permeability, probably of the order of

membranous glomerulonephritis. As a matter of fact, doubly refractive lipid bodies may be found in the urine (Munk). This type of lesion is not characterized by distortion of the architecture so that it conceivably could be quickly restored. The resistance of other forms of membranous glomerulonephritis to therapy is difficult to understand in the light of the response of the luetic nephrosis. The syphilitic nephrosis responds poorly to mercurial antiluetic therapy, well to arsenical therapy, and best to penicillin therapy (Barr et al.)

#### 4. Syphilitic focal interstitial nephritis

About a decade ago, a distinctive type of nonsymptomatic syphilitic damage to the kidneys of patients with secondary syphilis was described by Rich. Grossly, these kidneys showed glistening, greyish yellow flecks beneath the capsule and deeper in the cortex. These foci project from the cut surface very much as shining grains of sand. In later stages, these flecks may be associated with small irregular scars. Microscopically, the lesions are characterized by spherical nodules of interstitial inflammatory cells which invaginate the wall of a tubule into its lumen (plate 164). These inflammatory herniating knobs represent the constant feature of the lesion. The infiltrate consists of histiocytes, lymphocytes and rare plasma cells along with a few eosinophilic leukocytes.

The second prominent feature of the process is the presence in the tubular lumens of cholesterol crystals in the midst of lipid macrophages, other mononuclear cells, polymorphonuclear leukocytes, and cellular debris. Such foci may be rare or numerous but not so frequent as to interfere with renal function. The glomeruli are not altered unless they happen to be caught within the inflammatory areas where-in they, as well as the adjacent tubules, may become atrophic. There may be considerable perivascular infiltration of mononuclear cells but no significant intrinsic vascular alteration indicative of syphilis. It appears probable that a more advanced phase of the process is characterized by focal irregular scars. Unlike con-

A



FIG A Kidney of bubonic plague shows pallor and swelling.

FIG B Renal abscess in bubonic plague Numerous plague bacilli are present in the tubular casts

PLATE 159. PLAGUE

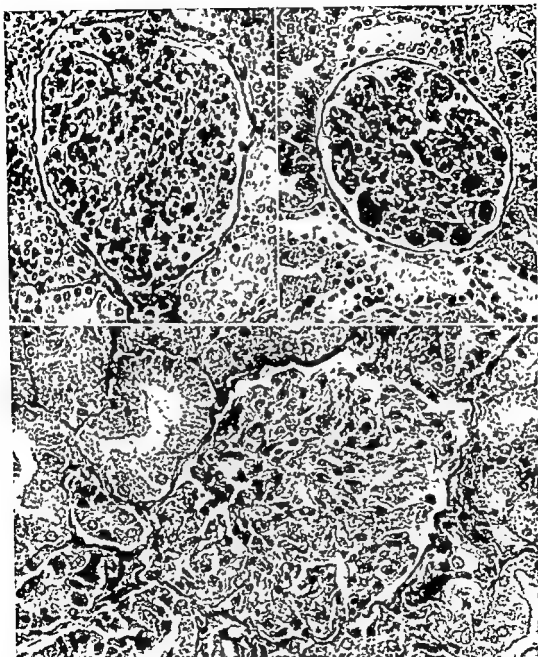


FIG. A *Acute diffuse proliferative glomerulonephritis in bubonic plague*

FIG. B. *Thrombi in glomerular capillaries due to dehydration and shock in bubonic plague*

FIG. C *Glomerulonephritis in cholera* Note the swollen thickened basement membranes of the ischemic glomerulus and the epithelial vacuolization of the proximal tubules (osmotic nephrosis). Another coarser type of vacuolization may also be observed (see plates 107 and 103)



A



B

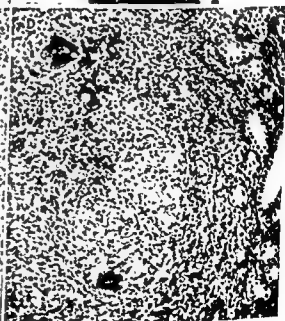


FIG A *Tuberculous pyelonephritis*

FIG B. *Miliary tuberculosis of kidney.*

FIGS C AND D *Miliary tubercles in kidney.*



FIG A *Hydronephrotic atrophy in caseous renal tuberculosis*

FIG B *Caseous tuberculosis of kidney selectively destroying the pyramids*

FIG C *Necrotizing papillitis simulating tuberculosis*

genital luetic nephritis which shows an abundance of spirochetes, as yet, spirochetes have not been demonstrated in these lesions, nor, it appears, in any other *acquired* luetic lesion of the kidney. Recently we have seen three instances of this lesion in the kidneys of *nonsyphilitic* white patients with varying degrees of pyelonephritis (plate 164). These latter lesions are indistinguishable from those described by Rich as specific. Nevertheless, this type of focal interstitial nephritis *does* appear to occur with a significantly higher incidence in syphilitic than nonsyphilitic patients. The possibility of the occurrence of a focal interstitial nephritis (and of perhaps other acute forms of lesions) as a result of a Herxheimer reaction cannot be excluded.

#### *Hemosiderosis and hemoglobinuric nephrosis*

Paroxysmal cold hemoglobinuria is a rare disorder which occurs chiefly in individuals with syphilis, generally of the congenital type. Its effect on the kidney is almost always inconsequential, consisting of hemosiderosis of the proximal tubules, as in Marchiafava-Micheli's disease. An instance of fatal hemoglobinuric nephrosis at least *associated* with paroxysmal cold hemoglobinuria has recently been reported (Sussman and Kayden). However, this case had complicating features so that hemoglobinuric nephrosis should not be considered an intrinsic part of paroxysmal cold hemoglobinuria.

#### RELAPSING FEVER

Relapsing fever is a louse- and tick-borne acute febrile disease caused by the diverse strains of borrelia, of which the most important are *B. recurrentis* (louse-borne) and *B. duttoni* (tick-borne). The organisms were originally regarded as treponemata but it is currently felt that they are likely to belong to the genus borrelia. For this reason, the inclusion of relapsing fever under "Spirochetal Diseases" is done with some license. The borrelia may be seen in blood smears stained routinely with Wright's or Giemsa's stains; they are about 10 to 20 microns in length, actively motile and have several broad coils.

The incubation period of relapsing fever about three to six days. The clinical picture the tick-borne form is characterized by a somewhat more severe course with more frequent relapses and complications than occur in the louse-borne disease. The onset in both types sudden with headache, remittent fever or prostration. The primary stage lasts several days to a week and subsides spontaneously. With each succeeding attack—usually one, two or more occur—the symptoms become less severe. Specific antibodies are present which decrease in titer after the paroxysms subside. The mortality rate is approximately 5 per cent. Pneumonia, anemia, jaundice, meningitis, an iritis are the common complications, in addition to focal interstitial nephritis and glomerulitis. The organisms may be demonstrated in both glomeruli and tubules, with or without slight associated lesions (plate 165A, B).

#### LEPTOSPIROSIS

Leptospirosis or Weil's disease is an acute infectious disease of dogs and humans caused by the spirochete, *Leptospira icterohemorrhagiae*. In humans the infection is highly virulent and the mortality is about 30 per cent. Undoubtedly the incidence of the disease is greater than generally indicated because Weil's disease is mistaken for other forms of hepatitis with jaundice. The rat is the reservoir of *Leptospira icterohemorrhagiae* but does not contract the

with the excreta of infected rats.

The clinical features of Weil's disease are those of severe infectious hepatitis, often with a complicating renal insufficiency. The incubation period is about 10 days after which headache, fever, prostration and myalgia especially of calf muscles occur. A hemorrhagic tendency is common in this initial stage during which the organisms may be recovered from the blood. This septicemic stage is followed by progressive recovery in the mild cases, but in the more severe ones jaundice develops frequently to an extreme degree. With the jaundice there may be associated the complete clinical syndrome of



FIG A *Caseous tuberculosis*, recent hematogenous dissemination with marked caseous component

FIG B *Healed tubercle* of kidney with central calcareous degeneration at right of photomicrograph

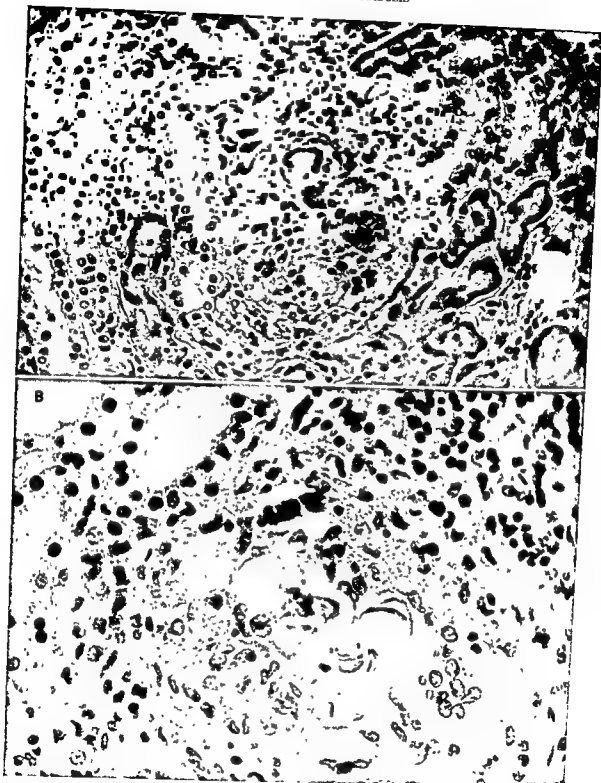
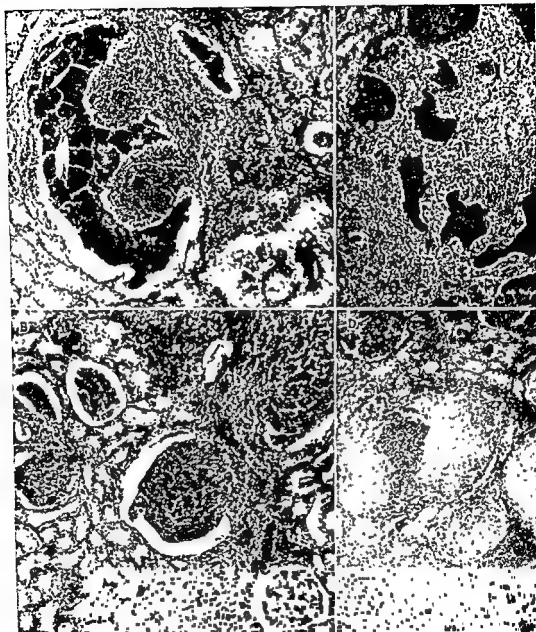


FIG. A *Sarcoidosis of kidney from a white female (aged 42) with classical generalized sarcoidosis. There was no renal dysfunction.*

FIG. B *Renal sarcoidosis with fragments of a Schaumann body in a tubercle. (From same case illustrated in figure A.)*



FIGS A AND B *Syphilitic (f) nephritis*, characterized by patches mainly of lymphocytes which bulge the walls of distal convoluted tubules into their lumens. Cellular debris and cholesterol needles occupy the lumen. The lesion is found in the secondary stage of syphilis, according to Rich. No spirochetes have been demonstrated in the lesions. Courtesy of Dr. A. R. Rich (A.F.I.P. Acc. 109392).

FIGS C AND D *Lesions of chronic nonspecific*

though the incidence of the change appears considerably higher in syphilitics.

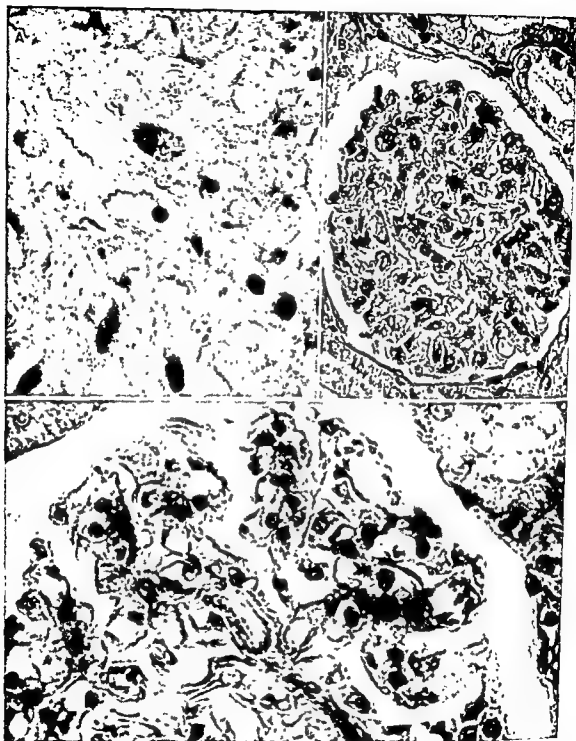


FIG. A *Treponemas* of relapsing fever in glomerular capillaries (Warthin-Starry stain)

FIG. B Mild proliferative glomerulitis in relapsing fever.

FIG. C. Larva of *canine filaria* in glomerulus



FIG A Interstitial nephritis due to infection of human by *Leptospira icterohemorrhagiae*

FIG B Focal interstitial nephritis from a syphilitic. The picture contrasts with that of figure A

FIG C *Leptospira icterohemorrhagiae* in proximal convoluted tubule of human kidney (Warthin-Starry stain) (A F I P' Acc. 64526)

FIG D *Leptospira canicola* in proximal convoluted tubule of kidney of a dog (Warthin-Starry stain)



hemoglobinuric nephrosis or severe cholemic nephrosis with oliguria or anuria and mounting azotemia. Renal insufficiency and jaundice are present between the ninth and sixteenth days and are accompanied by a high titer of specific antibodies. Iridocyclitis, meningitis and even leptospiral endocarditis may complicate the convalescence. It is of interest in connection with the renal picture, which may simulate hemoglobinuric nephrosis clinically and pathologically, that necrosis of voluntary muscle is reported as a common finding in Weil's disease (Sheldon). The common incidence of the myositis has been recently disputed, however. The hepatitis which is usually remarkably inconspicuous histologically, in contrast to severe symptoms, is responsible for the cholemic nephrosis, of course, but it may also contribute to the occasional instance of hemoglobinuric nephrosis after the, as yet, unclarified manner of other types of hepatitis.

In addition to cholemic and hemoglobinuric nephrosis, there commonly occurs a patchy interstitial nephritis, generally most marked in the corticomedullary region but also involving the cortex and medulla proper. The inflammatory cells consist predominantly of plasma cells along with lymphocytes and basophilic and acidophilic histiocytes. In dogs that remain carriers of leptospira, the interstitial nephritis persists for a long period and, in some instances, appears to be replaced by scars. Whether a corresponding lesion occurs in the human kidneys is not known. Frequently, onto the focal interstitial nephritis there is superimposed a cholemic (less frequently hemoglobinuric) nephrosis with serious compromise of renal function. Characteristic "C" or "S" shaped treponemas may be in the tubular lumens, particularly of the

disease, (2) endemic (murine) flea-borne typhus, (3) the spotted fever, tick-borne group, (4) the tsutsugamushi fever or scrub typhus group borne by the larval mite, and (5) a miscellaneous group including "Q" fever. The vaccines and the antibiotics, chloromycetin and aureomycin, have eliminated much of the dread of these diseases, which, in the past, have been responsible for literally millions of fatalities.

The causative organism is one of a variety of rickettsias which are identified by tests of their diverse antigenic properties, including the complement-fixation tests, the direct rickettsial agglutination and the Weil-Felix reaction against the OX19, OX2 and OXK strains of *B. proteus*. The rickettsias are transmitted by ticks, fleas or larval mites, their reservoirs are mice, rats or bandicoots. Brill's disease, murine typhus, Rocky Mountain spotted fever, rickettsialpox, and "Q" fever still occur in the United States. The epidemic, louse-borne typhus is a disease known to be smoldering in the Near East chiefly, but is present elsewhere including Mexico. The tsutsugamushi group is found in the Far East as is also "Q" fever. The spotted fever group of diseases is present in South America, Europe and Africa, as well as in the United States.

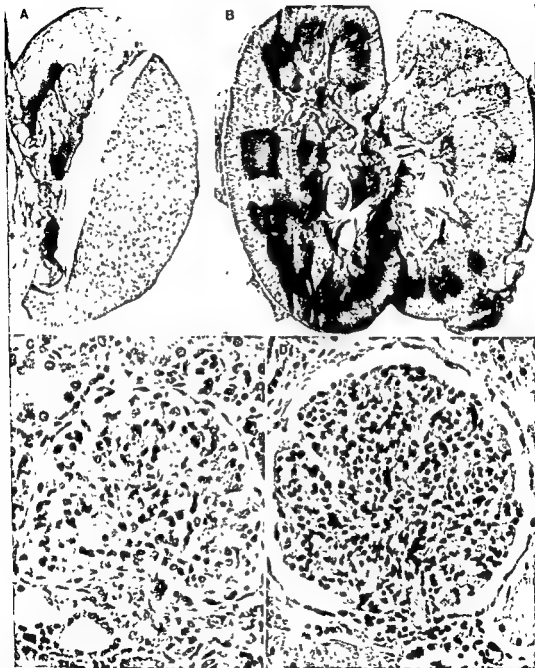
### Renal Picture

Renal complications have been observed in the epidemic typhus fever, Rocky Mountain spotted fever and scrub typhus. The clinical picture in these diseases is essentially similar and consists of headache, chills, fever, prostration, followed by a maculo-papular rash and, in severe cases, insomnia, delirium, convulsions, shock and vasomotor collapse. In spotted fever, hemorrhagic necrosis of the scrotum may occur; in scrub typhus, a primary lesion or eschar develops at the site in which the rickettsias are inoculated by the mite. Azotemia with oliguria is common in each of these diseases, especially in epidemic typhus (Yeomans et al.). Clinical investigators have attributed the azotemia to liver damage secondary to vascular involvement. This conclusion is completely without histologic foundation (Allen and Spitz).

## THE RICKETTSIAL DISEASES

### Introduction

The principal rickettsial diseases are, (1) epidemic, louse-borne typhus fever and Brill's



FIGS A AND B *Glomerulonephritis of epidemic (louse-borne) typhus fever with the hemorrhagic mottling commonly found in the kidneys of the typhus fevers*

FIGS C AND D *Acute diffuse proliferative glomerulonephritis of epidemic (louse-borne) typhus, a common finding in the typhus fevers (Am J Path III 603-681, 1945)*



FIG A Glomerulonephritis of Rocky Mountain spotted fever.

FIG B Arteritis and periarteritis in myocardium from a case of epidemic typhus fever

FIG C Arteritis in kidney in Rocky Mountain spotted fever. The renal arteritis is infrequent and rarely is responsible for renal dysfunction in any of the typhus fevers (*Am. J. Path.* 21, 603-651, 45).



FIG A *Acute interstitial nephritis in scrub typhus*

FIG B *Acute diffuse glomerulonephritis of scrub typhus*

FIG C *Phlebitis of renal interlobar vein in scrub typhus. Arteritis, except for the skin, is extremely rare in scrub typhus (Am J Path 21 603-631, 1945).*



FIG A Characteristic concentration of mononuclear cells (lymphocytes, plasma cells and histiocytes) in peritubular capillaries. The peripheral blood count showed merely a mild lymphopenia so that these cells represent a selective localization probably prior to interstitial deposition. A similar picture is found in nephritis from other causes (Am J Path 21 603-631, 1945).

FIG B Tubular degeneration and regeneration in a proximal tubule of kidney in scrub typhus. A mitotic figure is seen. This degree of change is unusual (Am J Path 21 603-631, 1945).

FIG C. *Rickettsias* of scrub typhus from splenic smear (Giemsa stain)



FIG A Marked interstitial nephritis of renal medulla from a case of hemorrhagic smallpox. The inflammatory cells are almost exclusively lymphocytes.

FIG B Hemorrhage in renal pelvis from a case of hemorrhagic smallpox. The kidney participates in the generalized hemorrhagic diathesis. Such a massive pelvic hemorrhage might simulate a neoplasm in a pyelographic roentgenogram.

Focal interstitial nephritis characterized by lymphocytes, plasma cells and basophilic histiocytes is common in all of the typhus fevers. It is quite the same quality of focal interstitial nephritis that is present in other infections, such as smallpox (plate 171A) and leptospirosis (plate 166A).

The kidneys, in a high percentage of cases show an early, reversible, but definite, acute diffuse proliferative glomerulonephritis. This change was found in 30 per cent of cases of scrub typhus, 50 per cent of cases of Rocky Mountain spotted fever, and 78 per cent of those with epidemic typhus. The glomerular lesions resemble those of acute diffuse glomerulonephritis described by Bell in 64.8 per cent of instances of subacute bacterial endocarditis. Cafferena found acute diffuse glomerulonephritis in 07.5 per cent of cases of epidemic typhus fever, a figure along with our own, that is much higher than those generally recorded (plates 107-170) (Allen and Spitz).

Despite the deeply entrenched cliché that the typhus fevers are yet another example of diffuse vascular disease, it must be emphasized that no extraglomerular lesions of renal vessels were found in the personal examination of over three hundred cases of scrub typhus. In epidemic typhus and Rocky Mountain spotted fever, visceral arteritis may be found (plate 168B, C) but the process is usually so sparse as to be functionally insignificant for all practical purposes, with the exception of the brain. This same disparity obtains between quantitative vascular involvement of viscera and the grave physiologic derangement attributed to the arteritis by most investigators of the typhus fevers. As a matter of fact, visceral arteritis in scrub typhus is almost always completely absent, nevertheless, in these cases, the clinical picture of sepsis is basically similar to that of epidemic typhus and Rocky Mountain spotted fever in which more frequent but still isolated arteritis is histologically overemphasized very much as it is in diffuse lupus erythematosus and scleroderma.

lesions in the kidneys of cases with spotted fever and epidemic typhus. As has been previously indicated (Allen and Spitz) the visceral lesions of the typhus fevers—e.g., the interstitial pneumonitis, the myocarditis, the necrosis of lymph nodes, the interstitial nephritis, the diffuse glomerulonephritis—are in all likelihood a reaction to allergens or toxins from the rickettsias rather than to the direct local action of the organisms themselves. As mentioned, the principles of allergy that apply to bacteria obtain just as intimately in the case of rickettsias and viruses.

### FUNGUS DISEASES

The fungi, including *Coccidioides immitis*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Cryptococcus neoformans* and *Actinomyces bovis*, may involve the kidney but are not responsible for any significant renal insufficiency with the occasional exception of the last named.

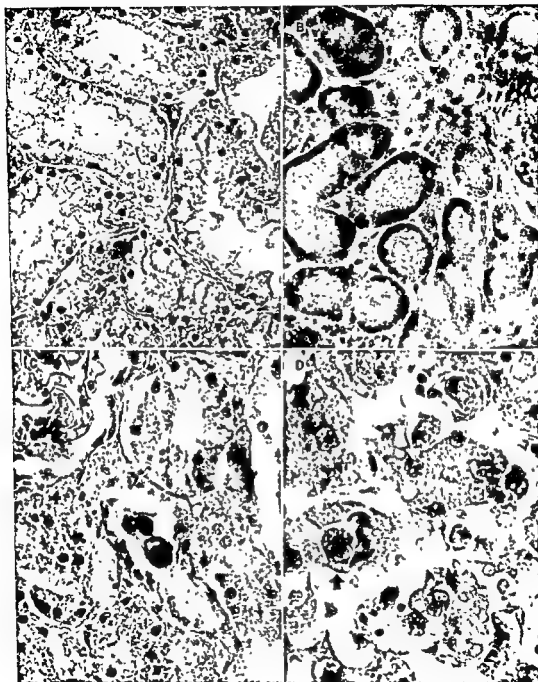
#### *Coccidioidomycosis*

*Coccidioidomycosis* occurs principally in the west and southwest of the United States. The first case in this country was described in 1896. The causative organism is the nonbudding, endospore-forming, doubly contoured, variable-sized fungus, *Coccidioides immitis*.

Two essential clinical pictures occur.

1. An evanescent self-limited *pneumonia* known also as Valley fever, dust fever, or San Joaquin Valley fever. This entity probably represents the entire reaction in a majority of cases and is associated often with *erythema nodosum*. The allergic nature of this phase of *coccidioidomycosis* is strongly suggested. Skin tests and complement fixation tests are strongly positive in this phase of pneumonitis. The organisms are not recovered in the sputum. No renal complications are attributed to this response, but the occurrence of occasional concomitant cases of acute glomerulonephritis would not be surprising.

2. The far more serious form of *coccidioidomycosis* is the *granulomatous stage*, representing endogenous spread. About 1 of every 500 cases of what is initially apparently allergic pneumonitis progresses to the fatal dissemi-



FIGS A AND B *Lapid vacuolization of epithelium of proximal tubules in kidney of yellow fever (Sudan III stain in figure B)*

FIG C *Anisotropic yellowish green crystals in distal convoluted tubules in yellow fever. These crystals resemble leucine*

FIG D *Councilman bodies (arrow) in hepatic cells in yellow fever.*



PLATE 173. FUNGI: COCCIDIIDOMYCOSIS

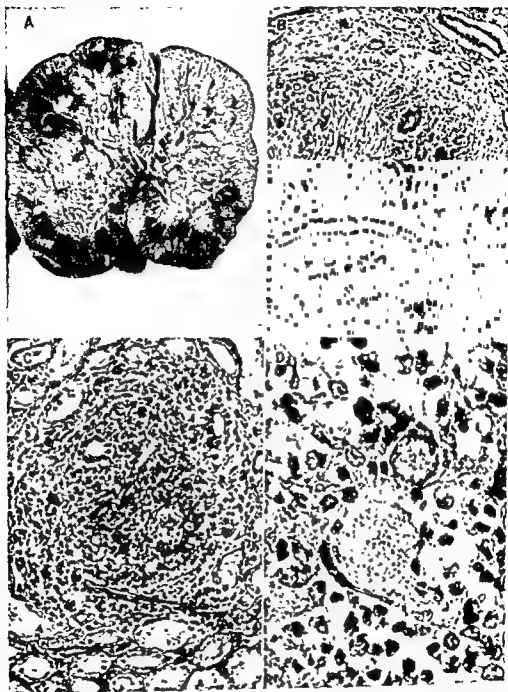


FIG A *Coccidioidomycosis* of kidney The greyish-white nodules represent coccidioidal granulomas, resulting from hematogenous dissemination

FIG C Spherules of *Coccidioides immitis* present in granuloma of figure B

FIG B Coccidioidal granuloma of kidney The granuloma consists of lymphocytes, macrophages, and giant cells with spherules of *Coccidioides immitis*.

FIG D Coccidioidal spherules showing double contour of capsule which encloses typical endospores Budding does not occur

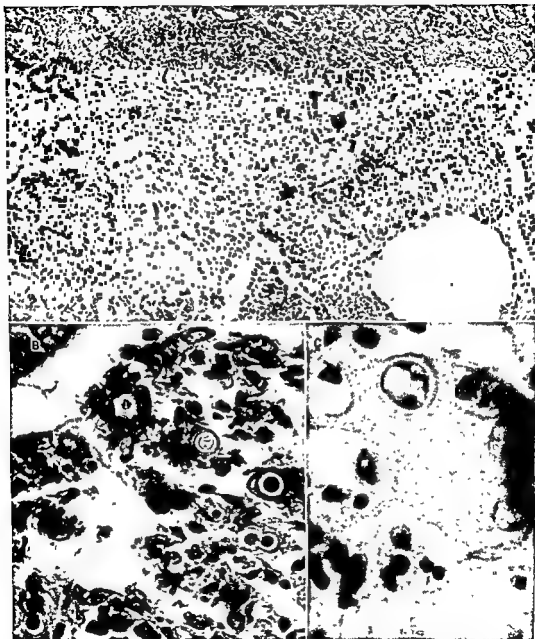


FIG A *Blastomycotic* giant cell granulomas in association with acute diffuse glomerulonephritis as evidenced by the glomerulus at the left. Higher magnifications are in figures A and B.

FIG B *Blastomycotic* spores, with budding. No endospore formation occurs in these cells in contrast to those of *Coccidioides*.

FIG C Spores of *Blastomyces dermatitidis* with doubly contoured capsule in a giant cell.

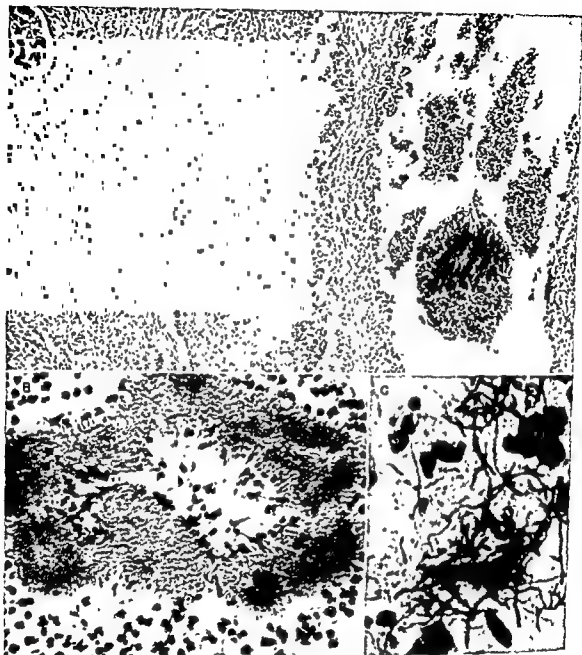


FIG A *Actinomycotic granuloma with the ray fungus at the right*

FIG B *Actinomyces bovis* under high magnification (paraffin section) The characteristic peripheral (acid-fast) clubs as well as the polymorphonuclear leukocytic reaction are seen

FIG C *Smear of actinomyces showing the typical branching forms (Gram stain).*

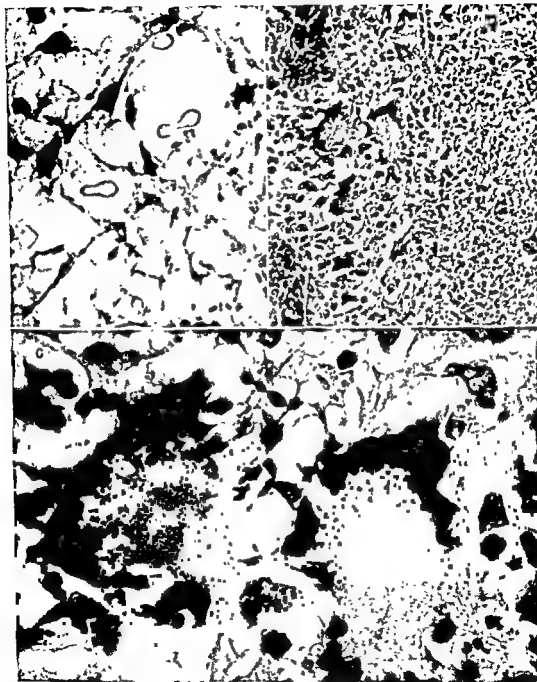


FIG A *Torula* (*Cryptococcus hominis*) may infect the kidney. Budding forms and large gelatinous capsules are shown.

FIG B Renal histoplasmosis showing giant cell granulomas.

FIG C *Histoplasma capsulatum* in giant cells, from renal histoplasmosis illustrated in figure B.



FIG A *Echinococcus* cyst showing dense capsules and daughter cysts

FIG B Daughter cysts of *Echinococcus granulosus*.

FIGS C AND D Detailed photographs showing hooklets of scolices of echinococcus cysts

nated granulomatous form. Clinically, roentgenologically and anatomically in the gross, the granulomatous phase of the disease, in all basic respects, is indistinguishable, or almost indistinguishable from the picture of tuberculosis. Even the coccidioidin skin test, as in tuberculosis, may become negative in the terminal phase.

The renal lesions take the form of minute or coalescent, hyaline or necrotic, miliary tubercles (plate 173). Histologically, the tubercles can not be differentiated from those of tuberculosis except for the finding of the specific organism. The spherule of *Coccidioides immitis* is usually about 20 microns in diameter but may be several times that. The walls are doubly-contoured and may enclose several or numerous endospores or potential spherules (plate 173 C and D). Usually the spherules are localized to the Langhan's giant cells of the tubercle. Occasionally non-specific vacuoles within the giant cells may be mistaken for fungi. No involvement of the renal pelvis or ureter was noted in 95 cases (Forbus and Bestebreurtje).

#### *Blastomycosis*

Blastomycosis (Gilchrist's disease), also called North American blastomycosis in contrast to South American blastomycosis (paracoccidioid granuloma), is another form of cutaneous deep fungus infection which may disseminate to involve any of the viscera. There is reason to believe that, as with coccidioidomycosis, the skin is not the only portal of entry, the respiratory tract appears to be an occasional primary site from which cutaneous and visceral systemization may follow. An evanescent pulmonary phase corresponding to the Valley fever of coccidioidomycosis has not been identified.

The renal histologic lesions are quite like those of coccidioidomycosis. The organism of *Blastomyces dermatitidis* is small, 5 to 12 micron, yeastlike, budding, nonendospore-forming spherule usually found within giant cells. Plate 174 illustrates a kidney with an acute diffuse glomerulonephritis in addition to the hematogenous granulomas of blastomycosis. The possibility of the pathogenesis of the glomerulo-

nephritis being allergic in nature and dependent on the blastomyces certainly cannot be gainsaid. The tubercles of blastomycosis tend to become purulent and necrotic. These tubercles may be indistinguishable from those of coccidioidomycosis or tuberculosis without demonstration of the etiologic organisms.

#### *South American Blastomycosis*

South American blastomycosis is limited chiefly to Brazil, Uruguay, Argentina, Venezuela and Peru. The disease is caused by the organism *Paracoccidioides brasiliensis*. The symptomatology and visceral lesions are similar to those of North American blastomycosis. The organisms (*Paracoccidioides brasiliensis*) are fairly large, 25 to 30 microns in diameter, and show multiple peripheral buds. Endosporeulation does not occur.

#### *Actinomycosis*

Actinomycosis, or lumpy jaw, is another wide-spread fungal granulomatous disease associated with visceral lesions. The causative organism is *Actinomyces bovis* or other species of this genus. The organism is usually introduced into the buccal cavity, but the skin of other parts of the body may be the portal of entry. In addition many instances of visceral involvement follow contamination of the peritoneal cavity during an appendectomy or as a result of spontaneous rupture of the appendix. As in the skin, burrowing sinuses steadily invade one viscus after another and make of the abdominal viscera an almost indissectable mass of riddled, matted organs. The kidneys, of course, participate in this process and extensive abscesses with pyelonephritis may occur. Grossly, the granulation tissue is likely to be distinctively yellowish because of the numerous lipid-filled macrophages in the granulomas. The grossly visible yellowish grey "sulfur" granules are several millimeters in diameter, these contain the ray fungus (plate 175).

Histologically, the ray fungus is composed of central Gram-positive masses of tightly entangled branching mycelial threads with a radial arrangement near the periphery and

clubbed ends at the tips. The ray fungus usually lies in a small pool of purulent exudate surrounded by granulation tissue with abundant histiocytes filled with fat. The previous uniformly fatal prognosis of this disease has been radically changed with the use, particularly, of the antibiotic, aureomycin.

### *Torulosis of Kidney*

Torulosis is a chronic infection produced by a yeastlike fungus named *Cryptococcus neoformans* or *Torula histolytica*. The disease is also known as European blastomycosis. The organisms are oval or spherical, budding, thick-walled cells surrounded by a mucicarmophilic gelatinous capsule (plate 176A). The organisms average about 6 to 12 microns in diameter, and they grow well on Sabouraud's agar or meat extract dextrose agar.

The organisms have a special affinity for the central nervous system, causing a chronic meningitis and cystic encephalitis. The portal of entry is probably the respiratory tract and the lungs may be involved. The kidneys are rarely affected in the spontaneous disease although renal infection occurs often in rats inoculated intraperitoneally with torulae (Jones). In isolated instances, visceral involvement in humans is found in the absence of cranial involvement.

The appearance of the kidneys grossly may resemble that seen in milary tuberculosis or milary coccidioidomycosis because of the scattered distribution of small grey nodules. Histologically, the fungi are found in glomeruli, tubules, or interstitium. Cellular reaction about the organisms may be absent or sparse or there may be a cyst or a nodule of lymphocytes and histiocytes which rarely are arranged in tubercle formation. Masses of the fungus may dilate individual tubules and in such instances, organisms are recoverable from the urine. Inoculation of mice by suspicious material reproduces easily identifiable lesions in many organs. As with blastomycosis and coccidioidomycosis, renal insufficiency is rarely caused by direct renal invasion of the fungi.

### *Histoplasmosis*

*Histoplasmosis* (Darling's disease), caused by *Histoplasma capsulatum* and other species, is a generalized mycosis characterized by fever, anemia, leukopenia, splenomegaly, hepatomegaly, pulmonary involvement and lymphadenitis. Renal involvement is infrequent. Involvement of the cardiac valves, adrenals, bones, and intestine with prominent ulceration may occur. It is felt that some of the calcific nodules generally dismissed as healed tuberculosis may actually represent healed granulomas of histoplasmosis. Such nodules, active or calcified, may be milary and may simulate milary tuberculosis of the lungs. Similar tubercles occur in the kidney without major dysfunction.

Histologically the lesions are formed of necrotic, caseous appearing centers with giant cells and various mononuclear cells at the periphery. The organisms are present particularly in the giant cells (plate 176B, C), but they also lie free or in single histiocytes. These fungi may be mistaken for leishmania but *Histoplasma capsulatum* is slightly larger, averaging 3 microns in diameter and has a more prominent nucleus located slightly off center. The kinetoplast and parabasal body of leishmania are, of course, not present.

### *ECHINOCOCCOSIS*

#### *Life History of Echinococcus granulosus*

The natural habitat of *Echinococcus granulosus* (*Taenia echinococcus*) is the intestine of the dog. Man (as well as sheep and cattle) acquire the infection by ingesting the ova, and the dogs, in turn, become infected from eating the viscera of sheep and cattle which contain fertile larval cysts.

The ova ingested by man hatch into hooked embryos which penetrate the portal circulation. The few larvae that are not filtered out by the liver may reach the lungs, brain, bones and other organs including the kidneys. The infection remains symptomatically latent for a long time in the final organ of localization. The immediate reaction of the host's renal tissue is active inflammation, presumably an allergic response to the larva. This reaction subsides as the leak of hydatid fluid becomes contained in



FIG. A. Acute diffuse glomerulonephritis in quartan malaria.

FIGS. B AND C. Tubular alteration in malaria. Figure B (*P. falciparum*) shows necrosis of epithelium of distal convoluted tubules in blackwater fever. In figure C the epithelium of proximal convoluted tubules is swollen with colloid or hyaline droplets or granules (quartan malaria).





FIG. A *Malarial (quarant)* glomerulonephritis showing fatty vacuolization of the epithelium of the proximal convoluted tubules. The patient presented a picture of the nephrotic syndrome.

FIG. B *Malarial pigment (falciparum)* in endothelial cells of glomerulus (arrows).

A

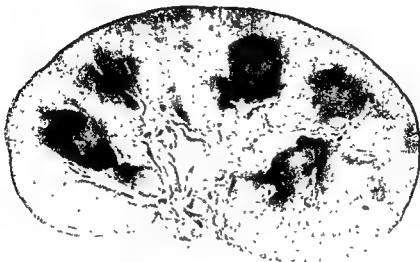


FIG. A. Kidney from a case of blackwater fever (*P. falciparum*) showing cortical swelling and congestion of the medulla.

FIG. B. Hemoglobinuric nephrosis of blackwater fever (*P. falciparum*).

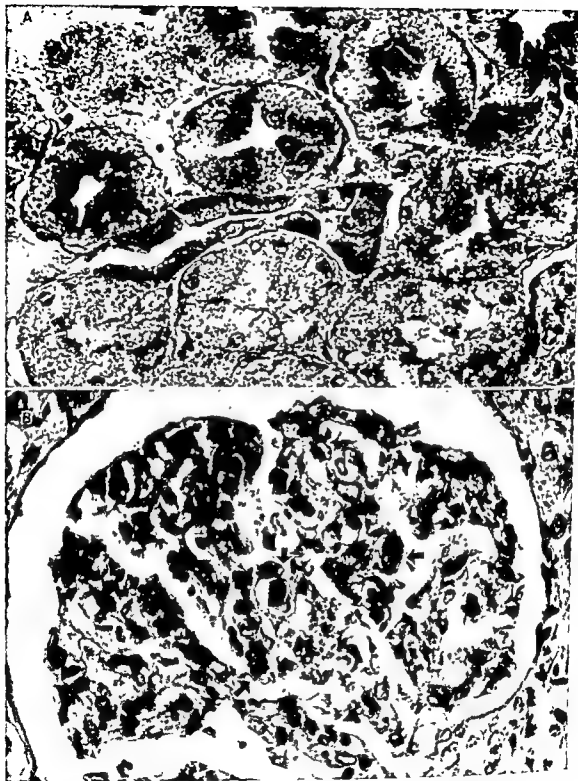


FIG A *Malarial (quartan) glomerulonephritis* showing fatty vacuolization of the epithelium of the proximal convoluted tubules. The patient presented a picture of the nephrotic syndrome

FIG B *Malarial pigment (falciparum)* in endothelial cells of glomerulus (arrows).

A

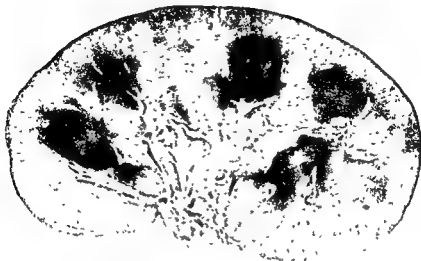


FIG. A Kidney from a case of blackwater fever (*P. falciparum*) showing cortical swelling and congestion of the medulla

FIG. B Hemoglobinuric nephrosis of blackwater fever (*P. falciparum*)

the adventitious nonspecific capsule of granulation tissue which encases a specific laminated hyalinized translucent wall. This laminated membrane is lined by germinal epithelium (plate 177). Frequently the cyst is unilocular and sterile, that is, without daughter cysts. The fertile cysts are those in which the germinal epithelium has given rise to brood vesicles lined by a single layer of cells from the inner surface of which scolices are formed. If the brood capsules are ruptured, the scolices are found in the hydatid fluid where they are referred to as "hydatid sand." Endogenous daughter cysts are formed from the invaginations of the wall of the mother cyst. Evagination of the same wall produces exogenous daughter cysts which may become separated from the mother cyst to form secondary hydatid cysts. A scolex consists of an anterior rostellar portion with four suckers and a double ring of hooklets. The scolices are characterized by highly refractile particles of carbonate of lime which often appear doubly contoured or laminated (plate 177C, D).

#### Clinical Picture

The renal involvement is often part of a generalized echinococcosis. Local symptoms are the result of pressure of the cysts. An instance of malignant hypertension secondary to involvement of a renal artery has been reported (Davison). Adherence to adjacent structures and rupture may lead to grave anaphylactic complications. Some of the cysts become ster-

ile, their growth ceases and they remain symptomatically latent. Others become inert through the effects of inflammatory and degenerative calcific changes. Calcification, *per se*, does not preclude vitality of the parasites (Reay and Rolleston). Those cysts that continue to grow may show the relentless expansion of a neoplasm.

#### Diagnosis

The echinococcus cysts of the kidney are usually single and vary from a few centimeters to a huge mass filling the accessible retroperitoneal space. The cysts occasionally rupture into the pelvis producing the picture of renal colic and pyelonephritis as the scolices and daughter cysts reach the bladder. These attacks may recur as the primary cyst closes and reopens. Rupture of the cyst into the pelvis may eliminate the daughter cysts and result in sterilization of the primary cyst. In the opened cyst, examination of the urine may reveal scolices and hooklets as well as pieces of laminated membrane. Palpation of a thrill by bimanual examination of the cyst is rare. Calcification of the wall of the cyst may be noted in roentgenograms as well as a "spider leg" deformity of the pelvis in urograms. Complement fixation and intradermal skin tests may be useful for diagnosis unless the cysts are so inactive that insufficient amounts of antigen are absorbed. The differential diagnosis includes neoplasms, other types of cysts, renal calculi, tuberculosis, hydronephrosis and acute abdominal diseases.

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# 10. Pyelonephritis

## Introduction

PYELONEPHRITIS, in one of its stages, is the most common renal lesion found at autopsy. This fact is hardly surprising in view of the large and diversified number of conditions that lead to pyelonephritis. These conditions include, along the hematogenous route, the many varieties and degrees of sepsis with renal localization, and, by the route of retrograde ureteral ascension, there is the long list of causes of obstruction of the lower urinary tract. Many instances of pyelonephritis are latent and discovered only at autopsy. Nevertheless, of the chief causes of contracted kidney, chronic pyelonephritis is more common than chronic glomerulonephritis and somewhat less common than benign nephrosclerosis.

Pyelonephritis, exclusive of the specific granulomatous diseases, such as tuberculosis, may be divided by pathogenesis and chronicity into:

### Hematogenous pyelonephritis

Acute

Subacute

Chronic

### Ascending pyelonephritis

Acute

Subacute

Chronic

There are observers (Weiss and Parker) who feel that it is impossible to know in a given case by which route the organisms reach the kidney. There are others (Mallory, Crane and Edwards) who are convinced that, even in the presence of ureteral obstruction, pyelonephritis is not effected by retrograde ascension of organisms, but rather that the organisms reach the kidney always by the lymphatic vessels, or by the blood stream. This concept may obtain in tuberculous nephritis, but its blanket application to suppurative pyelonephritis, in the presence of suppurative cystitis, ureteritis, and pyelitis, is doubted.

A major role of *pyelo-venous reflux* and *pyelo-*

*interstitial reflux* in the development of pyelonephritis has also to be proved. It is unquestionably true that retrograde pyelograms occasionally reveal radio-opaque material outside the calyceal and tubular system, in the interstitium, or in structures interpreted as veins. Tears of the mucosa by abnormal pelvic distention may account for some of the pictures, but a normal pyelo-venous communication is assumed to exist (Hinman). However, the relative paucity of renal pyelophlebitis, and particularly its distribution with regard to the foci of suppuration in acute ascending pyelonephritis, does not indicate a primary role of these veins in the dissemination of the renal inflammation. It is difficult to doubt that pyelonephritis by ascending spread of organisms does occur in addition to hematogenous pyelonephritis and that the two may be distinguishable in the acute stage, the scanty evidence for lymphangitic pyelonephritis does not seem to entitle it to the prominence which some have attached to it.

### Hematogenous Pyelonephritis

In the absence of obstruction of the urinary tract, pyelonephritis is assumed to be hematogenous. Weiss and Parker indicate, however, that physiologic obstruction may exert an effect equivalent to organic obstruction; on the other hand, the mere presence of organic obstruction not only does not preclude the hematogenous entry of organisms into the kidney, but actually renders such a kidney more susceptible to hematogenous localization during a bacteremia. Nevertheless, the fact that during an operation on the lower urinary tract, or following infection of this region, or even following catheterization of the urinary bladder, organisms may gain access to the blood stream and thence, in some instances, to the kidney, does not by any means disprove that ureteral ascension of infection may also occur.

### Obstructive Pyelonephritis

Obstructive pyelonephritis is a complication of pregnancy, ureteral calculi, strictures, aber-

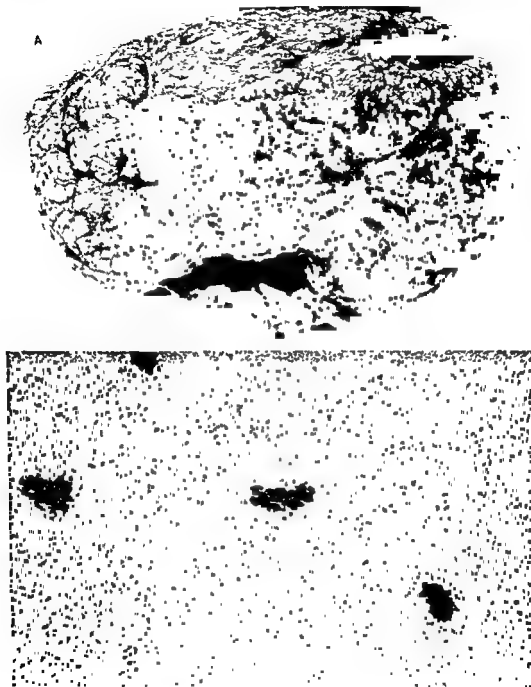


FIG. A. Acute hematogenous pyelonephritis in a case of *Staphylococcus aureus* septicemia. The light areas represent coalescent abscesses.

FIG. B. "Excretion" abscesses at cortico-medullary junction in acute hematogenous pyelonephritis. The black masses are clumps of staphylococci. The glomeruli show no histologic change. The patient was a 22 year old man with a *Staphylococcus aureus* sepsis.



A



FIG. A. Acute hematogenous pyelonephritis in staphylococcal septicemia. The diffusely scattered white dots represent abscesses which show no selective distribution.

FIG. B. "Excretion" abscesses of acute hematogenous pyelonephritis.

FIG. C. Purulent exudate in collecting tubules in acute hematogenous pyelonephritis. This field alone could not be distinguished from acute ascending pyelonephritis.

rant vessels, or neoplasms, metastatic or contiguous invasion of ureters or bladder by carcinoma of the rectum, uterus, or adnexae; hypertrophy or carcinoma of the prostate gland; tumors of the bladder, and spinal cord lesions. Acute pyelonephritis is particularly common in children, during pregnancy, and in old age. Banal chronic pyelonephritis in children, without any specific lesions of glomeruli or tubules, is responsible for renal rickets in a high percentage of cases (page 375). Robertson has stated that "almost every pregnant woman develops ureterocystitis and pyelocystitis" with urinary stasis during the second half of the gestational period, and about 1 to 6 per cent develop infections.

In from 60 to 80 per cent of cases, *Escherichia coli* is responsible for the infection; in the remainder, the organisms are *Aerobacter aerogenes*, *Streptococcus fecalis*, *Staphylococcus aureus*, and the genera proteus and pseudomonas. Bacteriuria may exist without any other evidence of pyelonephritis. It is obvious that the organisms may reach the blood stream secondary to an ascending pyelonephritis, just as they may secondary to ascending cholangitis following choledocholithiasis and suppurative choledochitis. At times, such bacteremia has been misinterpreted as cause rather than effect of ascending suppurative obstructive pyelonephritis.

#### *Clinical Picture of Pyelonephritis*

In the acute phase of hematogenous or obstructive pyelonephritis, there is fever, pallor, unilateral or bilateral lumbar tenderness, dysuria, tenesmus, pyuria, occasionally bacteriuria, slight to moderate anemia and other systemic signs of an acute infection. The blood pressure tends to be unchanged and no azotemia is likely to occur. The acute phase may subside and recur, and may result finally in the signs and symptoms of any severely contracted kidney. In this chronic phase, the symptoms obviously will vary with the extent of the scarring of the renal parenchyma. With advanced disease, the patient may show pallor, with some puffiness of the face but rarely with generalized edema, alkaline urine and slight hematuria. The concentration and dilution capacities and

the excretion of phenolsulfonphthalein may be impaired. Hypertension and azotemia may be present for years and may be characterized by considerable fluctuation. Weiss and Parker cite the case of chronic pyelonephritis that recovered from uremic pericarditis with adequate renal function for several years afterwards.

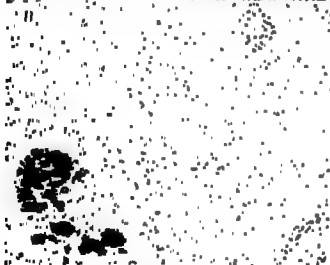
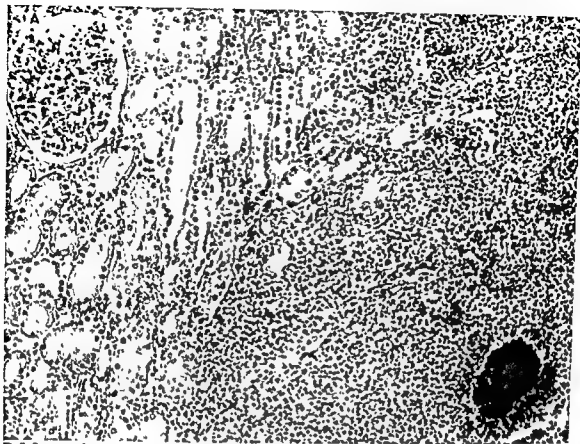
#### *Pathology of Acute Hematogenous Pyelonephritis*

##### *Gross appearance*

In acute hematogenous pyelonephritis, there are gross foci of suppuration distributed haphazardly chiefly through the cortex of the kidneys (plates 181, 182, 183). Often there is a rim of congestion about the yellowish-grey abscesses. The suppuration may present also as wedge-shaped infarcts with bases toward the cortical surface. This is the "pyemic kidney" of acute hematogenous or suppurative pyelonephritis. Occasionally the lesions may take the form of a multilocular abscess, or a honey-combed cluster of small abscesses, which are referred to as a *carbuncle* (plate 183C). Carbuncles are usually unilateral, and may follow a furuncle or cellulitis of the skin, or sore throat. The infection may rupture through the capsule, and produce a perinephric abscess. Perinephric abscesses may also arise independently of direct renal extension of suppuration through suppurative emboli, or by lymphatic spread.

##### *Histologic appearance*

Histologically, there are scattered abscesses that appear to have been initiated chiefly in the glomeruli and in the lumens of the tubules, although there is usually considerable interstitial infiltrate. In some cases, the abscesses are localized principally at the corticomedullary junction and contain central masses of bacteria (plate 183A). These have been called "excretion abscesses" on the apparently correct assumption that the bacteria reach the tubule by passing the glomerular filter without seriously injuring the glomerular capillaries. On occasion, however, concomitant acute diffuse glomerulonephritis may accompany the suppurative hematogenous pyelonephritis (plate 183A). In such cases, the acute diffuse glomerulonephritis



C



FIG. A "Erection" abscess of acute hematogenous pyelonephritis in association with terminal acute exudative glomerulonephritis. The cluster of bacteria simulates a colony of actinomycetes as shown in figure B.

FIG. B. *Actinomyces* in abscess of kidney showing superficial similarity of the fungus to the colony of pyogenic organisms present in figure A.

FIG. C. Carbuncle of the kidney shown here above may simulate a neoplasm. This lesion generally is the result of a hematogenous spread of organisms from a focus elsewhere, as a furuncle of the skin.

A



B



FIG A Congested, dull, dilated pelvis and calyces of acute ascending pyelonephritis associated with acute cystitis, ureteritis and hydronephrosis.

FIG B Acute ascending pyelonephritis with purulent exudate principally in the lumens of collecting tubules but also in the interstitium. Ureteral obstruction with acute ureteritis was also present.

PLATE 183. ACUTE SUPPURATIVE PYELONEPHRITIS (HEMATOGENOUS)

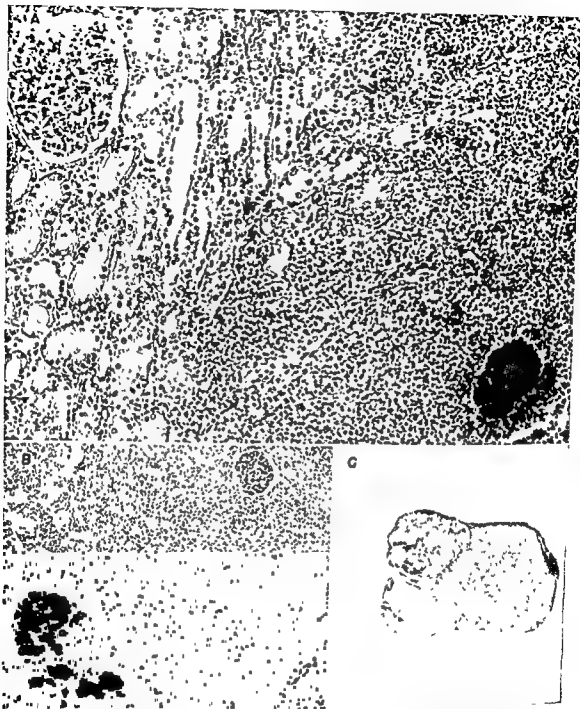


FIG A "Excretion" abscess of acute hematogenous pyelonephritis in association with terminal acute exudative glomerulonephritis. The cluster of bacteria simulates a colony of actinomycetes as shown in figure B.

FIG B Actinomycetes in abscess of kidney showing superficial similarity of the fungus to the colony of pyogenic organisms present in figure A.

FIG C Carbuncle of the kidney shown here above may simulate a neoplasm. This lesion generally is the result of a hematogenous spread of organisms from a focus elsewhere, as a furuncle of the skin.

PLATE 184. ACUTE SUPPURATIVE PYELONEPHRITIS (ASCENDING)

A

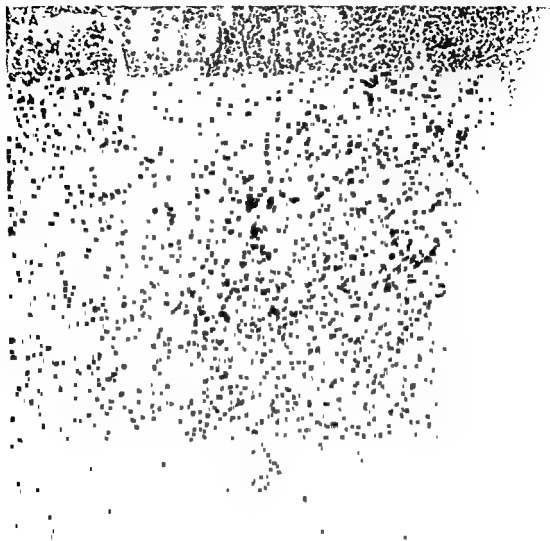


FIG A Congested, dull, dilated pelvis and calyces of acute ascending pyelonephritis associated with acute cystitis, ureteritis and hydronephrosis



FIG B Acute ascending pyelonephritis with purulent exudate principally in the lumens of collecting tubules but also in the interstitium. Ureteral obstruction with acute ureteritis was also present

PLATE 183. ACUTE SUPPURATIVE PYELONEPHRITIS (HEMATOGENOUS)





(Legends on facing page)



is assumed to be due, not to the direct local action of the organisms themselves, but, as in diffuse glomerulonephritis generally, to the action of the allergenic products of the organisms. Once again, this fact illustrates that more than one disease process may involve the kidney at the same time.

Acute hematogenous pyelonephritis is arbitrarily defined as lasting less than four months (Bell). Hematogenous subacute pyelonephritis showing resolution and organization is probably seen infrequently by the pathologist, and the chronic scarred phase is probably indistinguishable, by the pathologic picture alone, from other renal scars, especially those due to obstructive nephropathies.

#### *Pathology of Acute Ascending Pyelonephritis*

##### *Gross appearance*

There is usually obstruction with hydronephrosis in acute ascending pyelonephritis. In the ascending type, the mucosa of the urinary tract distal to the kidney, that is, calyces, pelvis, ureter and bladder, is likely to be hemorrhagic, granular, and obviously continuously infected from the site of obstruction and infection, upward to the kidney. The kidneys may be involved unequally, one kidney may be completely spared (plates 184, 185).

##### *Histologic appearance*

Microscopically, the picture resembles the hematogenous suppurative pyelonephritis except for the greater frequency of wedge-shaped infiltrations of the parenchyma with the apices at the calyces (plates 184, 185). The inflammatory cells are polymorphonuclear leukocytes with an admixture of lymphocytes and plasma cells. Many of the glomeruli in the involved areas are destroyed.

#### *Pathology of Subacute Ascending Pyelonephritis*

There is a trend to avoid the term "subacute" in the classification of diseases, including the nephritides. However, in the case of ob-

structive pyelonephritis there is fairly clear pathologic distinction between subacute ascending pyelonephritis on the one hand and acute and chronic ascending pyelonephritis on the other.

##### *Gross appearance*

In a longitudinal cut of the kidney, the more less sharp wedge of inflammatory reaction, with its apex extending from the tip of the papilla to a base beneath the cortical capsule, is uniformly pale greyish yellow and is usually rather clearly definable from the adjacent purplish brown normal parenchyma. No soft areas of suppuration are present and the consistency of the lighter areas is not different from the rest of the kidney. The capsule generally is not adherent to the cortex over these foci, the foci may be irregularly present throughout the kidney or only one or two may be present. The renal surface beneath the capsule is mottled yellowish grey to purplish brown corresponding respectively to the areas of inflammation and the normal or congested kidney (plate 186).

##### *Histologic appearance*

Histologically the sharp wedge of inflammatory reaction of subacute ascending pyelonephritis presents a prominent change (plates 186, 187A). Under low magnification, the compact mass of inflammatory cells may simulate the lymphosarcomatous or leukemic involvement of the kidney (plate 187B). The manner in which the inflammatory reaction fans out from the medulla to the cortex (a pattern which may be simulated by the lymphomas), the quality of the cells, the frequent fibrosis of Bowman's capsules often with unchanged malpighian tufts, and the pyelitis suggest inflammation rather than neoplasia. The inflammatory cells consist mostly of lymphocytes with scattered plasma cells and histiocytes, and a few polymorphonuclear leukocytes, the latter may occur in clumps in the distal tubules. In the areas of subacute pyelonephritis, the entire

FIG. A Granular purulent inflammation of obstructed dilated ureter and pelvis in acute ascending pyelonephritis

FIG. B Acute ascending pyelonephritis showing wedge-shaped distribution of exudate following its ascent from pelvis

FIG. C. Acute ascending pyelonephritis following ureteral obstruction.



(Legends on facing page)

PLATE 186. SUBACUTE PYELONEPHRITIS (ASCENDING)



FIG A Arterial nephrosclerosis (1), arterial and arteriolar nephrosclerosis (2), and subacute pyelonephritis (3) (on the right) The latter is illustrated further in figure B

FIG B Subacute pyelonephritis [from kidney (3) in figure A] The lymphocytic infiltrate, atrophy of tubules, normal malpighian tufts and slight thickening of Bowman's capsule shown above precede the final wedge-shaped scarring of chronic pyelonephritis

tubular structure shows evidence of advancing atrophy in contrast to the tubular hypertrophy of adjacent nephrons of the spared parenchyma, and in contrast also to kidneys with lymphomatous infiltrate closely collaring relatively normal tubules

### *Pathology of Chronic Pyelonephritis*

#### *Gross appearance*

The contracted kidney of chronic pyelonephritis is not always distinguishable from shrunken kidneys due to glomerulonephritis, arterial and arteriolar sclerosis, perarteritis nodosa, and multiple healed infarcts. Grossly, several features may aid in the differentiation: (1) the grey-white scarring of the pelvis and calyces, occasionally with pyelitis cystica (plate 190), (2) hydronephrosis, and (3) the presence of broad but shallow, irregular, U-shaped cortical depressions (plate 186A). The depressions tend to be U-shaped rather than V-shaped, as in infarcts, probably because of the greater rapidity of development and, often, the greater degree of atrophy in infarcted areas. Obviously there are exceptions to this rule. On cross section, the shallow cortical depressions may be seen as the bases of more or less wedge-shaped atrophic areas pointing to the calyces.

#### *Histologic appearance*

Histologically, the chronic inflammation of the pelvic wall may be observed. As a rule, however, there is no parallel between the degree of pelvic and parenchymal involvement in chronic pyelonephritis. The more important histologic features include: (1) cortical clusters of fibrotic glomeruli, especially within the wedges of atrophic areas, (2) disproportionate thickening of Bowman's capsule in contrast to the relative integrity of the malpighian tufts, (3) the presence of many "colloid" casts in the tubules, (4) interstitial fibrosis, and (5) endarteritis obliterans (plates 188, 189). This vascular change is perhaps part and parcel of the chronic inflammatory reaction in much the same sense as is the vascular sclerosis in the base of a chronic gastric ulcer or in the vicinity of other types of chronic inflammation. None of these features is by any means pathognomonic of chronic pyelo-

nephritis, but when integrated and weighed, they help establish the diagnosis.

### *Chronic Pyelonephritis and Hypertension*

The pyelonephritic kidney may develop considerable arteriosclerosis as well as arteriosclerosis, and in about 43 to 66 per cent of patients there may be an associated hypertension (Bell, Weiss and Parker, Longcope). The average cardiac weight in chronic pyelonephritis is 450 Gm. as opposed to 600 Gm. in the over-all group of malignant nephrosclerosis (Weiss and Parker). As in other kinds of renal disease with hypertension, malignant nephrosclerosis may supervene. That there is a pathogenetic tie-up between chronic pyelonephritis and hypertension is certainly suggested by the very frequent association of the two. It is therefore not unlikely that there is a pathogenetic relationship between chronic pyelonephritis and arteriosclerosis, just as there may be between chronic glomerulonephritis and arteriosclerosis. To pursue this thought one step further, when malignant nephrosclerosis occurs in association with these diseases, it is not an accidental superimposition occurring by sheer statistical chance any more than when it is superimposed onto benign nephrosclerosis. Clearly this is not the same as stating that arteriosclerosis is the cause of the hypertension.

the relief of the hypertension (page 412). In a far greater number of instances, this procedure has been fruitless. Possibly one reason for the general lack of success is the fact that arteriolar sclerosis is usually present in the "normal" kidney if the hypertension has existed for an appreciable length of time. Hence, in such cases, removal of the unilateral pyelonephritic kidney leaves the contralateral kidney with the vascular change that perpetuates the elevated blood pressure initiated by the abnormal kidney. Evaluation of the measure of success following nephrectomy for hypertension, at times striking, must be tempered with the realization that some relief of hypertension may occur after abdominal operations not related to the kidney (Volini and Flaxman).

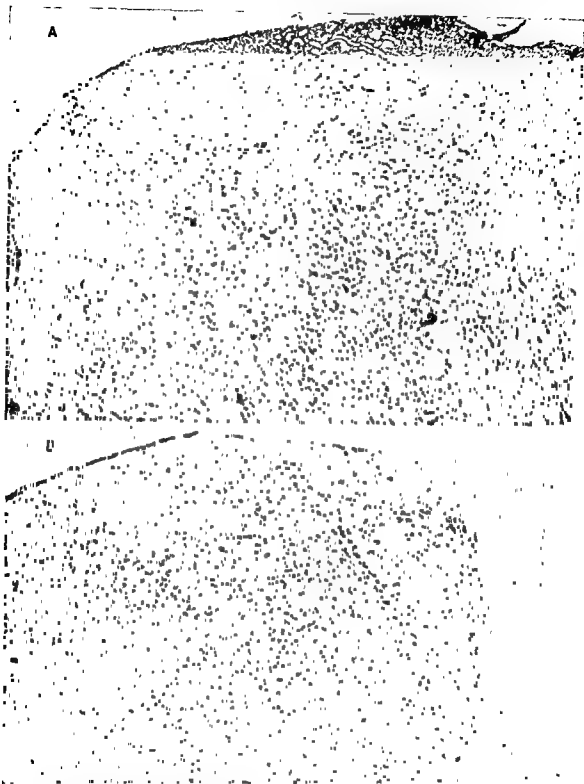


FIG A Subacute nonspecific pyelonephritis showing wedges of lymphocytic infiltration alternating with essentially normal parenchyma

FIG B Lymphocytic leukemic infiltrate (leukoma) simulating subacute pyelonephritis by virtue of the lymphocytes and the wedge-shape of the infiltrate.



FIG A Chronic nonspecific pyelonephritis showing characteristic features of (1) thickened capsule, (2) compact clusters of hyalinized glomeruli, (3) atrophy of tubules, (4) marked thickening of Bowman's capsule in striking contrast to the integrity of the glomerular tufts, and (5) colloid casts, only a few of which are present here. (A.F.I.P. Acc 91542)

FIG B Pelvis of chronic nonspecific pyelonephritis with conspicuous lymphocytic infiltrate

### NECROTIZING PAPILLITIS

In recent years so much emphasis has been given to a lesion called "necrotizing papillitis" that it has come to be regarded both as a clinical and pathologic entity (Edmundson, Martin, and Evans, Robbins, Mallory, and Kinney). The original description of the condition was made by Friedreich in 1877

#### Pathology

Grossly, the lesion is characterized by whitish or yellowish grey, friable necrotic foci sharply delimited to the pyramids which may be partially or completely replaced by these necrotic areas. One or more pyramids may be involved unilaterally or bilaterally, although the lesions tend to be widespread (plate 191A). *Histologically*, the lesion consists of dense purulent exudate within and between the collecting tubules and extending various distances up into the medulla (plate 191 B, C). The interstitial tissue and the tubular epithelium look ischemically infarcted. The periphery of the lesion, corresponding to the gross picture, is abruptly differentiated from the viable parenchyma. The vessels show no unusual change which might be considered responsible for the infarct-like lesion. Renal arteriosclerosis is common because papillitis occurs in more or less elderly diabetics, but certainly many instances of greater arteriosclerosis occur without the necrotizing lesion. Significant, primary thromboses are not noted, nor, in fact, are thromboses attributable to the inflammation seen in any appreciable degree. A lesion quite like necrotizing papillitis has long ago (1901) been produced experimentally with vinylamin (Levaditi), thalline, orthothalline and anathalline (Rehns). Levaditi's paper is a superb example of the integration of chemical and morphologic investigations.

#### Pathogenesis

Necrotizing papillitis is by no means a specific lesion of diabetes mellitus. Only about two thirds of the cases are found in diabetics, the lesion occurs in about 3 per cent of a sized diabetics. In all instances in diabetics, lesion appears associated with a severe ascending pyelonephritis; in non-diabetics, obstruction in the urinary tract is

cases. Precisely what the pathogenesis of this ischemic type of medullary necrosis is, remains unclear. It has been suggested that acutely increased intrapelvic pressure on the pyramids abetted by pressure of the interstitial purulent exudate on the peritubular capillaries may result in interference with the medullary blood supply. The pathogenesis of the experimental necrotizing papillitis (vinylamine and thalline) is equally nebulous

#### Clinical Picture

When the lesion is bilateral and involves most of the pyramids, it leads to rapidly progressive and fatal renal insufficiency, after a sudden onset with fever, leukocytosis, pyuria and often hematuria. A similar volume of infarcted renal tissue otherwise distributed might not cause such interference with renal function, but in this entity, the necrosis is strategically situated at the papillae where outflow is jeopardized. Sloughing of whole papillae has been described

In view of the apparent relationship of necrotizing papillitis to acute suppurative pyelonephritis, generally of the ascending obstructive type, considerable precautions should be taken when surgical procedures are contemplated on the genito-urinary tract of elderly diabetics, because of their vulnerability to infection. In addition to the chemotherapeutic measures, consideration should be given as to whether or not ureters from a diabetic patient should be transplanted to the infective area of the bowel rather than to the skin, despite some of the mechanical advantages to the patient of the former procedure. Another advantage of cutaneous transplantation of ureters in a diabetic patient is that glycosuria may be more readily estimated and controlled. The problem is of course an individual one but failure to weigh these factors has led to fatalities

PAR	ABSCESS
Paranephric extension of r sport of inf rating adj tion du	Its from (1) direct n, (2) lymphatic or from nous most



FIG. A Chronic pyelonephritis with colloid casts, atrophic glomeruli, interstitial lymphocytic inflammation, widened Bowman's space and thickened Bowman's capsule

FIG. B Chronic pyelonephritis with obvious disparity in degree of fibrosis of Bowman's capsule and the contained malpighian tufts

FIG. C Hyperplastic sclerosis along with colloid casts, thickening of glomerular capsule, dilatation of Bowman's space, interstitial fibrosis and arteriolar sclerosis





FIG. A. *Pyelitis and ureteritis cystica*

FIG. B. *Pyelitis cystica* with calcification of cystic contents.

FIG. C. *Pyelitis cystica*. The cysts are not the result of dilatation of Brun's nests but are formed by vesiculation directly within the epithelium.

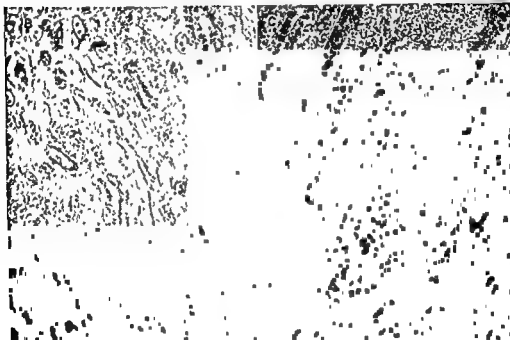


FIG. A. *Necrotizing papillitis* in a diabetic patient. The lesion may involve any or all of the papillae (courtesy Dr. W. A. D. Anderson).

FIG. B. *Necrotizing papillitis* showing the infarct-like type of necrosis (nondiabetic).

FIG. C. *Necrotizing papillitis* with extensive leukocytic infiltration in addition to bland necrosis (diabetic).

common route is from an abscess of the kidney. In any case, the therapy of the local abscess is independent of its pathogenesis.

The diagnosis of paranephric abscess is based on local pain, costo-muscular tenderness, irritation and spasm of the psoas muscle with resultant flexion of the hip joint, and systemic signs of infection. The pain may be referred to the hip joint and the contraction of the psoas may be taken to indicate a psoas abscess. The paranephric abscess may point in odd locations, such as Scarpa's triangle, above the iliac crest through Petit's triangle, and even through the diaphragm to cause pleural empyema. Because the paranephric abscess almost always causes perinephritis, there is abnormal fixation of the kidney in contrast to the opposite side. This feature of immobility may be demonstrated with pyelograms. The pyelogram may also be distorted by the abscess and may simulate a neoplasm.

### HYDRONEPHROSIS

#### Introduction

Hydronephrosis is one of the most common renal disorders and refers to the dilatation of the renal pelvis and calyces usually with atrophy of the parenchyma. The hydronephrosis may be partial or complete, that is, it may not affect all of the calyces. "Closed" or "open" hydronephrosis indicates respectively the complete or incomplete blockage of the ureter. In "intermittent" hydronephrosis, the nature of the obstruction is such that it is relieved periodically. The names "extrarenal" and "intrarenal" hydronephrosis indicate essentially that the dilated pelvis is extra- or intrarenal in location, this distinction serves very little purpose and is not to be confused with the process of "internal" hydronephrosis. The term "internal" hydronephrosis is used to designate the acute dilatation of tubules and Bowman's spaces with normal pelvis and calyces, secondary to intraparenchymal obstruction by crystals (sulfa, calcium oxalate) or casts (plates 142B, 192D), or the early phase in some cases of hydronephrosis due to external obstruction.

#### Etiology

The causes of hydronephrosis are congenital or acquired. The congenital causes include (1)

atresia of the ureter, (2) torsion, kink, stricture, or valve of the ureter, (3) anomalous artery with resultant compression or angulation of the ureter, (4) urethral stricture, diverticulum, or valve, and (5) functional or neuromuscular hydronephrosis in which autopsies disclose no organic obstruction, and in which paralysis of the ureterovesical sphincter, or possibly ureteral achalasia appears to be at fault.

The acquired form of hydronephrosis is produced by calculi, tumors of the ureter, extensions from carcinoma of the prostate, bladder, uterus, ovary, rectum, hypertrophy of the prostate, urethral abnormalities, uterine fibroids, retroperitoneal tumors, pregnancy, ureteral strictures, ureteral transplantations, accidental ureteral ligation, trauma to kidney or ureter, nephroptosis in relation to an accessory artery, pelvic inflammatory disease, and cord bladder secondary to spina bifida, tumors, syphilis, myelitis, amyotrophic lateral sclerosis, multiple sclerosis, or a trauma to the spinal cord. As stated, according to Robertson, "almost every pregnant woman suffers from ureterectasis and pyelectasis (hydronephrosis) from about the beginning of the fifth month of pregnancy to a few weeks after delivery." In most instances, the hydronephrosis, if uncomplicated, rapidly subsides after gestation.

#### Clinical Picture

Unilateral hydronephrosis may be clinically silent or its only symptoms may be those of a mass and the effects of compression by the mass. The symptoms are essentially those caused by complications. These are pyogenic infection, hemorrhage into the sac, infrequently rupture of the sac, renal insufficiency in the presence of an abnormal contralateral kidney,

hydronephrosis, as a group, than in control groups. This is so despite the ability to produce acute hypertension with reduction of renal blood flow in dogs by the ligation of one ureter (Levy et al.) Isolated cases of the relief of hypertension in humans after removal of a hydronephrotic kidney have been reported. As a rule the hypertension with hydronephrosis is associated with other renal diseases, such as benign nephro-

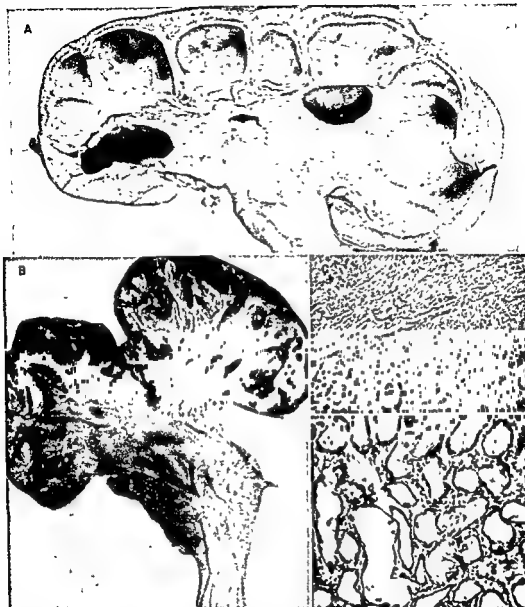


FIG A *Hydronephrotic atrophy* due to constriction at ureteropelvic junction. The ureter is of normal diameter. The pyramids are naturally reamed out before the cortex because of the direction and application of the hemodynamic vectors. (A F I P. Acc. 15217)

FIG B *Hydronephrosis with hydronephrotic ureter* due to obstruction by neoplasm at distal end of ureter.

FIG C *Capsular thickening and adherence* in hydronephrotic atrophy.

FIG D. *Acute internal hydronephrosis* secondary to obstruction by crystals of calcium oxalate in ethylene glycol (antifreeze) poisoning.

sclerosis, chronic pyelonephritis, and chronic glomerulonephritis.

### *Pathology and Pathogenesis of Hydronephrosis*

#### *Gross appearance*

Statements vary as to the effect of ureteral obstruction on the kidney. The best evidence is that with sudden complete obstruction and resultant closed hydronephrosis, the kidneys may undergo atrophy with over-all diminution in size (in rare cases). According to Hinman, such atrophy may follow not only complete hydronephrosis but also partial and intermittent hydronephrosis. However, he stresses that this type of atrophy of the kidney is an exceptional occurrence in both man and animals and that, except for these rare instances, the kidney enlarges with hydronephrosis after ureteral obstruction. The frequency with which the pancreas and salivary glands shrink after obstruction of their main ducts indicates a response of these organs strikingly different from that of the kidney. In the case of all three organs, the abrupt cessation of secretion or glomerular filtration after obstruction would seem to be the simplest and most reasonable explanation for the primary atrophy. Urologists disagree, however, and place great importance on the unique role of pyelorenal backflow.

The large hydronephrotic sacs follow open or intermittent obstruction with some degree of renal function persisting along with the progressive dilatation. Those huge closed hydronephrotic sacs that appear to follow complete occlusion are probably associated early with intermittent or incomplete occlusion. In the intermittent hydronephrosis, part of the contents of the sac is discharged from time to time with some relief of symptoms, after which the sac is refilled. The fluid in the closed sac is not altogether of constant composition, since some excretion and, perhaps, absorption takes place continually. Pyelovenous, tubulolymphatic, pyelolymphatic and interstitial backflow contribute to this interchange, according to Hinman. These forms of backflow which are stressed almost exclusively by urologists and roentgenologists, are often suggested by radiographic shadows indicative of urovenous backflow after retrograde pyelograms. Some ob-

servers attribute the backflow to ruptured veins or lymphatics; others, such as Hinman, point to the analogous resorption of aqueous humor from the anterior ocular chamber into the veins of the sclera without apparent communication.

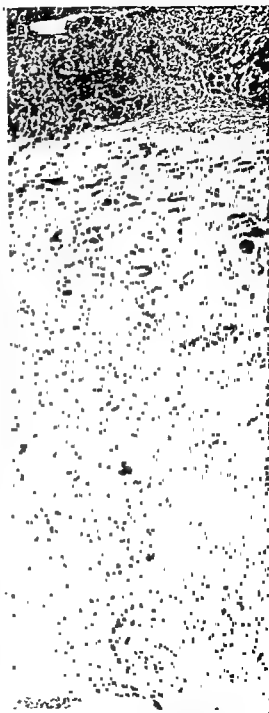
With obstruction, the pelvis dilates. A pelvis with a capacity greater than 10 cc constitutes a hydronephrosis. In extreme cases the sac may be distended to the size of 10 liters. The pressure of the fluid enclosed in the renal pelvis gradually obliterates the pyramids and compresses the columns of Bertin (septae) (plate 192A). With further atrophy, the cortex is reduced in thickness, and the surface of the kidney becomes bosselated as the lobes are reamed out. Eventually the septae are obliterated and all that remains of the kidney is a thin fibrous pouch.

The normal contralateral kidney undergoes progressive hypertrophy concurrently with the hydronephrotic destruction of the opposite kidney. The explanation of this compensatory hypertrophy is included in the theory of renal counterbalance. Experimentally, if one kidney of a dog is left intact and the other obstructed, no permanent repair follows the removal of the obstruction after 45 days, and very little after 30 days (Hinman). According to the theory of renal counterbalance, the compensatory hypertrophy of the intact kidney eliminates the need, so to speak, for the obstructed kidney to repair itself. On the other hand, removal of one kidney with the production of simultaneous closed hydronephrosis of the other, results in fatality in 14 days in most animals. If the nephrectomy is delayed a few weeks, however, many dogs survive when the hydronephrosis of 21 days duration is relieved. If a gradual "autonephrectomy" is produced by incomplete obstruction of the ureter, the opposite kidney with a completely closed hydronephrosis of 30 to 40 days duration may be so stimulated to repair after removal of the obstruction, as to perform adequate total renal function.

In other words, the degree of repair of a hydronephrotic kidney after contralateral nephrectomy depends on when, in relation to the onset of hydronephrosis, nephrectomy is performed despite the originally equal damage



110 A Calculous hydronephrotic atrophy with hydronephrotic and ureteral pseudo-valve formation



110 B Marked hydronephrotic atrophy of kidney showing entire remaining width from pelvis to capsule reduced to a thin rim



## II. Renal Calculi

### *Incidence*

RENAL calculi are present in about 5.4 per cent of all autopsies (Rosenow). However, most of these are instances of small, incidental calculi not productive of clinical symptoms or significant renal damage. In approximately 0.4 per cent of autopsies, the renal calculi are directly responsible for death either because of extensive pyelonephritis with uremia, or as a result of complications after operations for the calculi. Renal stones are infrequent in the early decades, about 1 per cent of cases occur in children under 10 years of age and may be associated with renal rickets. Approximately 50 per cent of cases are in the age group of 30 to 50 years (Randall). In Bell's series, the maximum incidence was between the ages of 50 and 75 years. In most series, there is a predominance of occurrence of calculi in males, the ratio being about 4 to 3 (Bell). The stones were somewhat less common on the right side than the left side in Bell's series and occurred bilaterally in 30 per cent of his cases. The preponderance of their occurrence on one side over the other varies with different series and it appears likely that the difference is not statistically significant. The 30 per cent incidence of bilaterality of stones is higher than the clinical figure of 8 per cent usually quoted, but Bell's data come from autopsies in which small, clinically undetected calculi are discovered. There is a greater likelihood of bilaterality of stones if the calculus in one kidney is branched rather than unbranched.

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Calculi may lie dormant for many years. Small stones may be passed in the urine periodically. Bell records one patient who passed more than 300 calculi over a period of four years.

The diagnosis of renal calculi may be established by the clinical picture supplemented with data from urinalysis for crystals, calcium (Sulkowitch test) and evidence of infection, by intravenous urography, by retrograde instrumentation, by pyelograms with contrast media and by lateral pyelograms.

### *Causes of Renal Calculi*

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With regard to urostasis, it is reported that a factor in the production of renal stones in natives of India is their incredible ability to refrain from micturating for days at a time (Roberts, Begg). Deficiency in vitamin A is responsible for abnormal keratinization of epithelium in a variety of locations, including bronchioles, pancreatic ductules, skin, and the urinary tract. The solitary stones in the urinary bladder in Syrian boys have been attributed to





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## Incidence

are present in about 5.4 per cent of autopsies (Rosenow). However, most instances of small, incidental calculi are not productive of clinical symptoms or renal damage. In approximately 0.4 per cent of autopsies, the renal calculi are discoverable for death either because of pyelonephritis with uremia, or as complications after operations for the stones are infrequent in the early years of life. 1 per cent of cases occur in children under 5 years of age and may be associated with rickets. Approximately 50 per cent are in the age group of 30 to 50 years. In Bell's series, the maximum incidence is between the ages of 50 and 75 years, there is a predominance of calculi in males, the ratio being 3 to 1 (Bell). The stones were somewhat more numerous on the right side than the left side and occurred bilaterally in 30 per cent of cases. The preponderance of their occurrence on one side over the other varies in different series and it appears likely that there is not statistically significant difference in the incidence of bilaterality of renal calculi than the clinical figure of 8 per cent quoted, but Bell's data come from much smaller, clinically undetected series. There is a greater likelihood of stones if the calculus is branched rather than unbranched.

## Clinical Picture

Calculi produce attacks of dysuria, hematuria, colic with local or radiating pain, and anuria. The colicky pain occurs when the stone passes down the ureter or obstructs the ureteral lumen. The attacks occur at irregular intervals varying from a few days to months. The anuria may be initiated by a warning of pain. The anuria of the kidney is attributed to reflex sup-

pression of function. "Reflex anuria" is a very real phenomenon, and is reproducible experimentally. The anuria with renal calculi is always a serious complication, and frequently proves fatal in from 4 to 16 days, as with anuria from other causes. The obstructing calculi may be in the pelvis or ureter. Not all renal calculi cause significant obstructive renal damage.

Calculi may be dormant for many years. Small stones may be passed in the urine periodically. Bell records one patient who passed more than 300 calculi over a period of four years.

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## Causes of Renal Calculi

Some of the causes of renal lithiasis are: primary and secondary hyperparathyroidism, bone diseases, idiopathic hypercalcaemia, chronic stasis with infection in the urinary tract, gout, cystinuria, oxaluria, xanthinuria, phosphaturia, and possibly vitamin A deficiency, and excess of vitamin D, or ertron (Kaufman). The cause of the largest number of cases has been attributed to idiopathic hypercalcaemia (Albright and Reifenstein). It is generally believed that hyperparathyroidism accounts for 0.1 to 0.2 per cent of renal stones, although Albright and Reifenstein place the incidence near the high figure of 3 per cent.

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deficiency in this vitamin (Brown and Brown) It is this type of association that has prompted the therapeutic and prophylactic use of vitamin A in patients with calculi The results have not been encouraging

### *Composition of Renal Calculi*

Calculi are composed chiefly of carbonates, amorphous and crystalline phosphates, oxalates, uric acid and urates Infrequently calculi are made up of xanthine, cystine, foreign bodies, fibrin, bacterial masses, and rarely indigo, cholesterol and fatty urosteoliths

The so-called primary stones tend to form in faintly acid or neutral urine These include stones of uric acid, urates, oxalates, xanthine and cystine The "secondary" calculi are precipitated in alkaline urine; these are calculi of ammonium magnesium phosphate and amorphous calcium carbonate and phosphate

Most large calculi are mixed, they are usually constructed of a nucleus of one chemical, often uric acid or urates, with outer coats of carbonates and phosphates (plate 195) Actually, a stone of pure chemical composition does not occur although those stones containing 90 per cent of one substance are loosely called pure Data on the chemical make-up of the nucleus of a calculus are of more value with regard to the determination of the etiology than information about its peripheral composition The nature of calculi differs in various parts of the world, principally because of diet For example, oxalate stones are especially common among the vegetarian Japanese (Hieman)

### *Methods of Analysis of Calculi*

There is a growing impression that chemical analysis of renal calculi offers no significantly

accuracy of data from routine chemical analysis of calculi

Some of the basic reasons for the gross defects of chemical analysis of stones are (1) the invalidating interference with the standard reactions by organic substances of unknown composition, (2) the technical barriers against the chemical resolution of complex mixtures com-

monly found in calculi, (3) the quantitative limitations of chemical study of very small calculi, and (4) the confusion regarding the exact nature of the reactions in the qualitative chemical tests (Prien and Frondel)

To eliminate these sources of error, Jensen and later Prien and Frondel have borrowed a technique from mineralogy which, with a polarizing petrographic microscope, permits an analysis of calculi by virtue of characteristic optical properties of crystalline substances. This method has been supplemented with the x-ray diffraction procedure in which finely powdered calculous material is irradiated by a beam of monochromatic x-rays, the rays diffracted from the planes of the crystals are recorded in varying intensity and spacing on a photographic film Inasmuch as no two compounds have identical crystalline structures, their x-ray diffraction patterns are as individualistic as finger prints The disadvantages of this method are the expense of the apparatus and the complexities of the subject matter These are practical disadvantages of consequence and currently limit the use to specialized investigative work (Prien and Frondel). The diffraction patterns of crystalline substances found in urinary calculi are illustrated in plate 196

It is of interest that renal calculi which have already formed may be made radioactive Benjamin and his associates demonstrated radioactivity in phosphate calculi in the renal pelvis after administering  $P^{32}$  orally.

### *Morphogenesis of Renal Calculi*

The most favored hypothesis of the morphogenesis of calculi is that suggested by Randall. In effect, he believes that calcification in the region of the renal papillae (Randall's plaques) serves as a nidus for the subsequent accretion of calcareous material (plate 204A). The calcified nidus eventually separates itself from the papilla and lies free in the calyx or pelvis to accrue further material, possibly after the manner of formation of stones in a focus of cholelithiasis in the gall bladder, or of pearls in an oyster. The observation of small calculi still attached to Randall's calcific plaques at the apex of the papillae is evidence in favor of this mode of origin of at least some of the calculi.

A



B



C



FIG. A. Portion of staghorn calculus in kidney with hydronephrosis and chronic pyelonephritis

FIG. B. Calculous pyelonephritis

FIG. C. Koenigsmannogram of staghorn renal calculus (KFP)



# CRYSTALS OF RENAL CALCULI



Triple and  
Amorphous  
Phosphates



Calcium Phosphate  
and Dumb-Bell  
Calcium Sulfate



Ammonium  
Biurate



Sodium  
Acid  
Urate

## URIC ACID CRYSTALS



Calcium Oxalate



Cystine



Leucine Spheres  
and Tyrosine  
Needles



Cholesterol



Calcium  
Sulfate



Hippuric  
Acid



Fatty  
Acids



Sulfapyridine









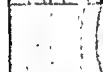

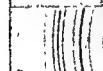

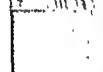

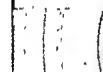

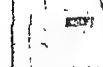
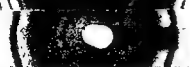


Sulfathiazole



Sulfadiazine



		Monetite Calcium Acid Phosphate
		Oxamide Diamide of Oxalic Acid
		Sod. Acid Urate
		Struvite Magnesium Ammonium Phosphate Hexahydrate
		Uric Acid
		Weddellite Calcium Oxalate Dihydrate
		Whewellite Calcium Oxalate Monhydrate
		Whitlockite Tricalcium Phosphate
		Xanthine

*X-ray diffraction patterns of various renal calculi. Each pattern is characteristic of the individual chemical composition of the stones. (Courtesy of Drs. E. L. Prien and C. Frondel, J. Urol. 87: 913-931, 1961.)*

It is doubtful if metastatic calcification of the distal convoluted tubules of itself leads to pelvic calculi by extrusion of the small foci. Only when the parenchymal nephrocalcinosis extends to the collecting tubules in the papillae, does it probably contribute to the formation of calyceal and pelvic calculi. Moreover, as Albright and Reifenstein point out, hyperparathyroidism may lead to the formation of pelvic calculi, as it often does, without any appreciable calcification of the distal convoluted tubules, and vice versa.

Undoubtedly, another less overtly mechanical factor is responsible for the formation of renal calculi, namely, the physico-chemical situation occurring when the urine is supersaturated with crystalloids. The crystalloids are held in a state of dispersion by adsorption to protective colloids. With supersaturation of the urine by excessive excretion of crystalloids, however, the normal colloidal mechanism fails to maintain solution and there is precipitation or gelling of the urinary colloids which form the calcular framework. The role in the formation of calculi played by necrobiotic debris resulting from infections and the keratinous material from epidermalization of the pelvic mucosa is not clear although generally assumed to be of importance.

#### *Complications of Renal Calculi*

The complications of renal calculi are (1) pyelitis, (2) pyelonephritis, (3) hydronephrosis, (4) anuria, (5) spontaneous rupture of the kidney, (6) renal lipomatosis, and (7) carcinoma of the renal pelvis.

Some calculi—even the large staghorn stones—may produce simple chronic pyelitis without involvement of the renal parenchyma. However, chronic pyelonephritis with hydronephrosis is the common result of persistent renal calculus or of renal calculi that have descended to the ureter. Instead of hydronephrotic obstruction and dilatation, the kidney may atrophy with a progressive increase of pelvic fat and perirenal fat referred to as lipomatosis (plate 278C). The deposition of fat may be considerable and may clinically simulate a renal neoplasm. Instances of kidneys with "calculous lipomatosis" are reported in which the kidneys

weighed over 1000 Gm. (Bell). In one series of 33 cases of renal lipomatosis, 26 were associated with calculi.

The association of carcinomas of the renal pelvis with calculi as in the case of the urinary bladder, appears more than coincidental. The calculi and associated infection tend to provoke a leukoplakia or dyskeratotic squamous cell metaplasia of the epithelium which, in the urinary tract, has a greater tendency to neoplastic change than does the normal epithelium (plate 310, 311). Rarely, the stones are associated with mucus-producing adenocarcinomas (plate 315).

#### *Treatment of Renal Calculi*

In most cases, obstructive ureteropelvic calculi, which produce symptoms, evidence of destruction of renal parenchyma, stasis or infection, should be removed operatively by nephrotomy, pyelotomy, or hemi- or total nephrectomy. It is true that some stones, formed in either alkaline or acid urine may be completely dissolved by appropriate dietary means, supplemented with vitamins A and D. However, the results are inconstant (Higgins) and should perhaps be reserved for calyceal calculi. The remarkable effect of dietary therapy has been to reduce the rate of frequency of recurrence of renal calculi following operative removal from 16.9 per cent to 2.9 per cent (Higgins). The recurrent failures on the dietary regime occur principally in those patients in whom the urinary pH resists control because of the presence of urea-splitting bacteria in the pelvis. Good results in the attempt to dissolve renal calculi have been obtained by Suby and Albright with the retrograde instillation of citrate solutions at a pH of approximately 4.5, made less irritating with the addition of magnesium oxide. This method was found practical for calculi composed of calcium phosphate, calcium carbonate and magnesium ammonium phosphate. Hyaluronidase has recently been tried with indifferent success although it has been suggested by Keyser and his associates that certain other enzymes, particularly uricase, give promise of beneficial effects when used in conjunction with the citrate solutions. The aim of the enzymatic therapy is to dissolve the organic matrix which



FIGS. A, B, AND C. Calcification of collecting tubules at apex of pyramid in association with pelvic calcinosis secondary to hyperparathyroidism. In figures B and C it is noted that the basement membranes of the tubules and the adjacent stroma are encrusted with calcium. This degree of calcification in this strategic outlet for the urinary flow may lead to serious renal dysfunction.

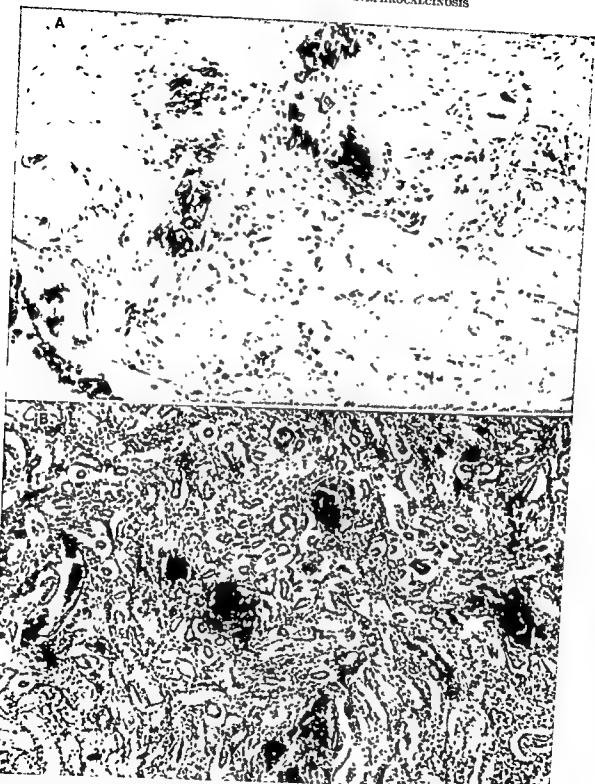


FIG A Uric acid microcalculi, collecting tubules and epithelium of a pyramid from a case of gout. The usual giant cell reaction is absent. (Compare plate 153)

FIG B Parenchymal nephrocalcinosis ("metastatic calcification") This same picture is produced by alkalosis, hyperparathyroidism, and extensive metastasis to bones (above). The black masses of calcium are in the lumens and epithelium of the distal convoluted tubules. The calcification may be as widespread as illustrated here without detectable interference with renal function.

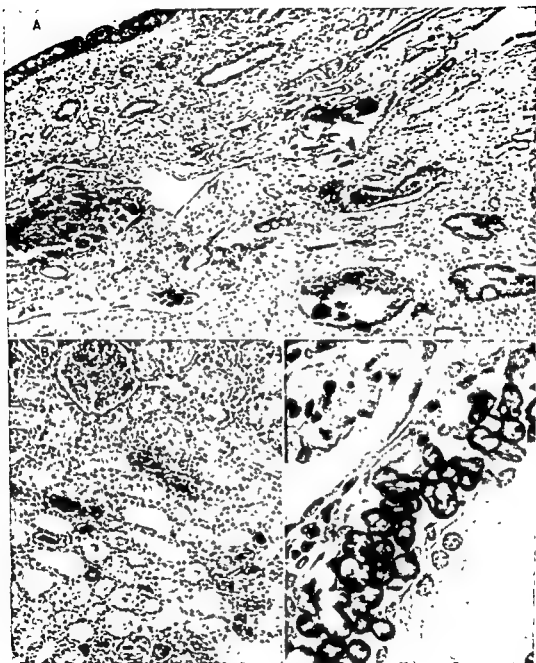


FIG. A. Calcification of tubular epithelium and calcium casts in the lumens of collecting tubules as a result of severe alkalosis.

FIG. B. Calcification of epithelium of distal convoluted tubules in alkalosis. The renal function was normal. The proximal tubules are altogether spared in contrast to the effect of mercuric bichloride.

FIG. C. Enormous calcification of epithelial cells in distal convoluted tubules in alkalosis. The calcified cells are sloughed and coalesce into calcium casts.

resists the solvents useful for crystalline components. Much of the infection associated with renal calculi can now be controlled with antibiotics. Adjustment of metabolic deficiencies, including correction of excessive calcemia and the use of abundant fluids are therapeutic adjuvants.

## PARENCHYMAL NEPHROCALCINOSIS

### *Introduction*

Alkalosis following vomiting or excessive ingestion of alkali, or "metastatic" calcification as a result of hyperparathyroidism, severe osteoporosis from trauma, prolonged immobilization, osteomyelitis, lytic osseous metastases, as from breast cancers or lymphomas, all lead to a qualitatively similar histologic picture in the parenchyma of the kidney. This lesion may be termed "parenchymal nephrocalcinosis" in contradistinction to grossly evident calculi in the renal pelvis. The calcification may occur in a very short time, alkalosis may produce it in several days. There is not necessarily a direct correlation between the extent of the osseous metastases and the degree of renal calcification. Undoubtedly the rapidity of the release of the calcium is a major factor in its disposition by the kidneys. It has been suggested that testosterone commonly produces renal calcification. In the cases at our disposal in which renal calcification has occurred with testosterone therapy, the renal calcification could be accounted for by the osseous metastases from the mammary carcinomas that were being treated.

### *Histologic Appearance*

With the rarest exception, the tubular change in metastatic calcification or alkalosis is clearly limited to the distal convoluted segments. The granules of calcium are deposited directly within the nuclei particularly (plate 199C), but extend also to the cytoplasm of the epithelial cells of the distal tubules (plate 199B). The nuclei are often sharply outlined by the calcification. Cellular debris is desquamated into the tubular lumens as calcareous casts.

The calcification is a bland process generally provoking no noteworthy inflammatory reaction. Occasional exceptions occur, however, in which mild leukocytic and epithelial response

takes place in the form of regeneration or syncytial fusion so as to simulate a foreign body giant cell (plate 151D). This latter formation in association with calcification resembles the tubular picture of multiple myeloma from which it may be easily distinguished by the absence of typical proteid casts of myeloma in other tubules and the presence of torpid calcification of individual epithelial cells in others. If the tubular epithelial necrosis in alkalosis is marked, it is likely that basic contributory complications, such as shock and dehydration are associated with the alkalosis and may not be given proper weight in the final evaluation. This kind of complication following excessive vomiting appears to have occurred in a case reported as "lower nephron nephrosis" due merely to alkalosis (McLetchie).

As a rule, as stated, the calcium is localized to the distal convoluted tubules and is therefore usually confined to the cortex (plate 198B). In this situation, parenchymal nephrocalcinosis rarely interferes with renal function to any significant degree. However, in the literature, partial to complete renal dysfunction has been attributed to such nephrocalcinosis, despite evidence to the contrary in the form of normal urea clearance tests (Kirsner and Knowlton). This fact is especially pertinent in the exaggerated role attributed to the even lesser degree of histologic tubular damage seen in some cases of hemoglobinuric nephrosis. In exceptional cases, however, the calcification which is in the region of the collecting tubules of the papillae produces partial to complete occlusion of their lumens, destruction of epithelium, and considerable renal insufficiency. The tendency to attribute renal insufficiency merely to the calcification is provoked by the sheer conspicuousness of the change and is as unjustified as it would be in the case of extreme hemosiderosis (plate 124B). Finally, no morphogenetic relation of parenchymal nephrocalcinosis, exclusion of calyceal calcification, to gross, pelvic calculi has been demonstrated.

In exceedingly rare cases in which massive amounts of calcium are liberated to the blood stream, the basement membranes of glomerular capillaries, Bowman's capsules and the walls of arcuate, subarcuate, and interlobular arteries

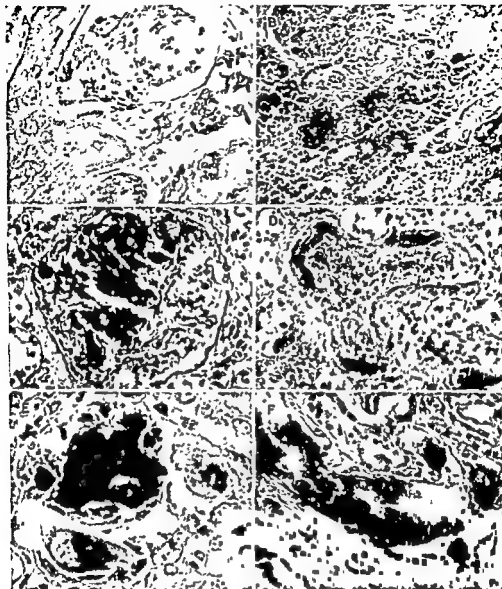


FIG. A Mammary carcinoma, metastatic to vertebrae, leading to renal calcification as shown in figure B

FIG. C Glomerular calcification of capillary basement membrane in hyperparathyroidism

FIG. E Metastatic calcification of a tubular cast of kidney in a case of multiple myeloma

FIG. B Calcification of epithelium of distal convoluted tubules from the case of mammary carcinoma illustrated in figure A

FIG. D Metastatic calcification in the wall of interlobular artery in hyperparathyroidism

FIG. F Calcification of necrotic tubular epithelium due to sulfonamide toxicity





FIG A. Two foci of ossification (arrows) in cysts in case of chronic nonspecific pyelonephritis

FIG C Ossification of apex of pyramid in hydronephrosis.

FIG B. Ossification of tubular casts from a case of multiple myeloma

FIG D Ossification of pelvis in hydronephrosis  
In each of the above cases, the ossification is of a metaplastic rather than dysembryogenic nature

PLATE 202. PARENCHYMAL NEPHROCALCINOSIS DIFFERENTIAL

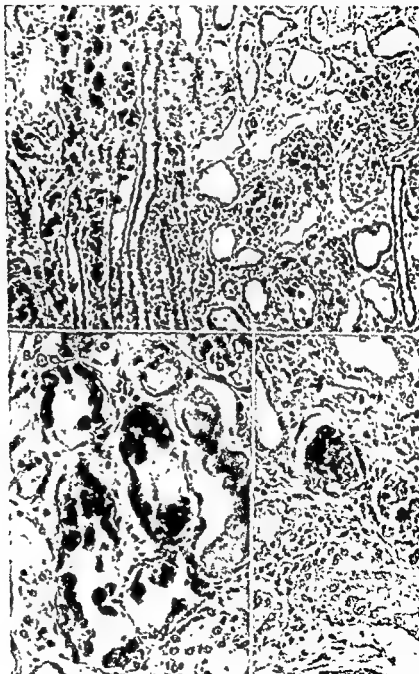


FIG. 3. Mercury dichloride nephrosis with extensive calcification confined to the distal tubules.

may all become more or less calcified. In this circumstance, calcification of the pulmonary alveolar septa, and of the gastric mucosa, and even of the hepatic parenchymal cells may be anticipated. The basement membranes of the collecting tubules and adjacent interstitium are not infrequently calcified (plate 197).

### *Differential Diagnosis*

The practical differential histologic diagnosis of parenchymal nephrocalcinosis (alkalotic or metastatic calcification) includes hyperparathyroidism (plate 200C, D), mercurial nephrosis (plate 202A), sulfonamide nephrosis (plate 202C), metastatic carcinoma to bones (plate 200A, B), myeloma nephrosis (plate 200E), and rare forms of acute diffuse glomerulonephritis with tubular calcification (plate 202B). The calcification in mercurial nephrosis and in acute glomerulonephritis is localized to necrotic epithelium of the proximal rather than the distal tubules. The calcification of sulfonamide nephrosis, metastatic osseous carcinomatosis, and myeloma nephrosis is really the equivalent of alkalotic or metastatic calcification superimposed on other changes, described elsewhere, which are produced in these conditions. The particularly revealing feature of alkalotic or metastatic calcification is the tendency for the exquisite outlining of the epithelial nuclei by the basophilic calcium. Finally, as previously indicated, alkalosis may occur with shock or other associated circumstances which, rather than alkalosis, may be responsible for the prominent epithelial regeneration and renal dysfunction. It is obviously unwarranted, in such instances, to attribute the tubular change and renal dysfunction solely to alkalosis.

### HYPERPARATHYROIDISM AND THE KIDNEY

Hyperparathyroidism may be (1) primary or (2) secondary. Primary hyperparathyroidism is caused either by hyperplasia, or adenoma, or, in rare instances, by carcinoma of the parathyroid glands. Secondary hyperparathyroidism results from hyperplasia of the parathyroid glands provoked by renal insufficiency. It follows that a neoplasm of the parathyroid gland producing a state of primary hyperparathyroid-

ism may be responsible for the cycle of nephrolithiasis, pyelonephritis, renal insufficiency and resultant hyperplasia of the other parathyroids or secondary hyperparathyroidism.

In the primary or secondary hyperparathyroidism, there is hypercalcemia with hypercalciuria, hypophosphatemia (with normal urea clearance), increased serum alkaline phosphatase in the presence of bone lesions, with polydipsia, polyuria, nocturia, often with increased excretion of chloride and base. Hypercalcemia itself may produce symptoms of muscle weakness, decreased excitability, constipation and vomiting, anorexia and skeletal pain.

The stimulus to parathyroid hyperplasia in renal insufficiency was formerly thought to be the hypocalcemia caused by retention of phosphates, in accordance with the law of the products of solubility. The current thought is that the regulator of the hyperplasia is the hypophosphatemia; the injection of phosphates in animals leads to parathyroid hyperplasia (Drake et al.).

In a very high percentage of cases (52, or 81 per cent, of 64 cases of Albright and Reifenstein) hyperparathyroidism is associated with parenchymal nephrocalcinosis or pelvic lithiasis often in association with osteitis fibrosa cystica or generalisata and occasionally with osteosclerosis (Ginzler and Jaffe). However, hyperparathyroidism may occur with or without renal calcinosis, and with or without bone disease. Occasionally, hyperparathyroidism, with hypercalcemia and nephrocalcinosis, may be simulated by lytic metastatic carcinomatosis—particularly rapidly developing metastases—to bones such as may occur with mammary carcinomas. In the case illustrated in plate 200A, B, the level of serum calcium was 22.4 mg. No significant renal insufficiency was present, incidentally, despite the widespread renal calcification.

### *Histologic Changes in Parathyroids in Hyperparathyroidism*

The histologic features of the parathyroid of primary hyperplasia, secondary hyperplasia and adenoma are not quite as sharply distinctive as treatises on the subject would indicate.

A



FIG. A. *Parathyroid adenoma*. Usually the residual cap of the original parathyroid gland may be observed. All patients with renal calculi should be investigated for hyperparathyroidism.

FIG. B. *Parathyroid adenoma* (from tumor illustrated in figure A) composed of broad sheets of water clear cells with scattered acidophilic cells.

FIG. C. *Parathyroid adenoma* (from tumor illustrated in figures A and B) composed of cords of acidophilic cells and ectopic areas.

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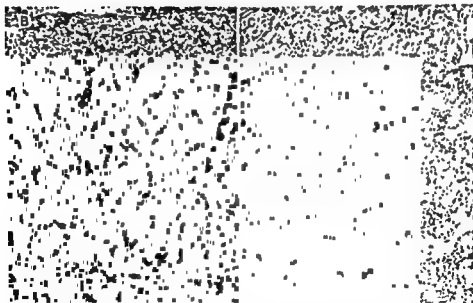


FIG. A *Parathyroid adenoma*. Usually the residual cap of the original parathyroid gland may be observed. All patients with renal calculi should be investigated for hyperparathyroidism.

FIG. B *Parathyroid adenoma* (from tumor illustrated in figure A) composed of broad sheets of water-clear cells with scattered acidophilic cells.

FIG. C *Parathyroid adenoma* (from tumor illustrated in figures A and B) composed of cords of acidophilic cells and conspicuous stroma.



(Legends on facing page )

As a rule, however, the following details are fairly characteristic:

### Adenoma

1. Most commonly, one gland, but occasionally only a portion of a gland or multiple glands are involved (in about 6 per cent of cases) (Norris).
2. The adenoma is usually composed not only of the chief (principal) cell but modified chief cells, that is, water-clear ("wasserhelle") cells, oxyphil cells or a mixture of cell types may occur, as in the case illustrated in plate 203.
3. The adenomatous cell is generally larger than normal, often with giant and multiple nuclei.
4. Fat is scanty and the fibrous stroma is irregular in distribution.
5. In Norris' 317 cases collected from the literature, there was a female predominance of 3 to 1 when single adenomas were present and 4 to 1, when multiple.

### Carcinoma

Carcinomas of the parathyroid gland are most uncommon and functioning carcinomas are extremely rare, but do occur (Black and Ackerman).

### Primary hyperplasia

Primary or idiopathic hyperplasia of the parathyroid glands is also a very infrequent

finding. All of the glands are likely to be enlarged, greyish white, soft, and poorly delimited. The hyperplastic cells are the water-clear cells and they tend to be enormously hypertrophied to from 10 to 40 microns in diameter. An alveolar pattern is common and actual microcysts may occur.

### Secondary hyperplasia

1. The parathyroids in secondary hyperplasia, as a rule, are creamy grey rather than brown, smaller, firmer and more variable than the adenoma, carcinoma or the parathyroid gland of primary hyperplasia. Usually each of the glands is involved.
2. The cell usually involved is the dark chief cell and is usually of normal size, without nuclear alteration.
3. There is an absence or diminution of interstitial fat.
4. The proportion of oxyphil cells is higher than would be expected for the age of the patient.
5. The glycogen content of the cells is somewhat greater than that of the cells of adenomas or of primary hyperplasias.
6. The normal columns of two to three cells tend to be broadened.
7. The pattern of cords may be focally altered to form compact areas, acini and papillary areas (Castleman and Mallory).

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FIG. A. High magnification of calculus of calcium phosphate in hyperparathyroidism. The laminated secretions appear to have been deposited on a Rand all's plaque. (Courtesy of Dr. W. A. D. Anderson, *Pathology*, C. V. Mosby, and *J. Urol.* 44: 29, 1940.)

FIG. B. Parenchymal nephrocalcinosis of kidney in primary hyperparathyroidism, caused by a parathyroid adenoma. (Courtesy of Dr. W. A. D. Anderson, *Pathology*, C. V. Mosby, 1948.)

FIG. C. Common tubular microcyst with calcified crystals and amorphous granules of calcium. Such calcified cysts are fairly common, without any relationship to hyperparathyroidism. They may be grossly visible as minute yellow flecks.



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## 12. Renal Rickets

### *Introduction*

Disturbances in ossification come not only from dietary deficiency, inadequate sunshine, and loss of calcium and vitamin D in bile and possibly hepatic diseases, but also as a result of diseases of the kidney. Children with chronic renal disease are inclined to be retarded in growth and to manifest osteodystrophic changes that are generally termed "renal rickets." Renal rickets (renal dwarfism, osteoneuropathy, renal infantilism) is then a clinical syndrome characterized by dwarfism, skeletal deformities of rickets that are refractory to antirachitic therapy (e.g., rachitic rosary, bowing of skull, bowing of legs), occasional retardation of sexual development, distinctive biochemical changes in the blood and urine, and renal disease of various kinds. As just indicated, the renal lesion associated with renal rickets is not a specific one, but includes any disorder of the kidney in childhood sufficiently severe to interfere with renal function. In this category are included hypoplasia, congenital polycystic kidneys, chronic glomerulonephritis, chronic pyelonephritis and hydronephrosis. In addition, renal rickets occurs with ill-defined renal lesions as in some instances of the de Toni-Fanconi syndrome, about which more will be mentioned.

The biochemical changes are essentially a disturbance in the relationship of calcium and phosphorus. In general, the changes include hypocalcemia, hyperphosphatemia, hypercalcemia, acidosis and azotemia. The bone lesions, in addition to those of dwarfism and rickets, are those of osteitis fibrosa cystica. These latter changes are caused by hyperparathyroidism secondary to the renal insufficiency. Calcium is thereby depleted from bones, and additional increments of calcium are lost by the combination of ingested calcium with phosphates excreted

by the intestine to form unabsorbable calcium salts. In some instances, the renal background of the bony changes may be latent so that operations have been performed on bones under the mistaken impression that the osseous lesions were primary. The disturbance in renal metabolism may be so profound as a result of the renal disorder that an astonishing premature calcification of large arteries may occur.

### *Variants of Renal Rickets*

The biochemical changes of renal rickets are not altogether constant and naturally there has been some attempt at further segregation of the cases on the basis of biochemical data. For example, Albright and Reifenstein emphasize the distinction between "renal rickets" and renal acidosis. They attribute the latter to "tubular insufficiency without glomerular insufficiency" although they admit the pathologic findings in the kidney are obscure. There is at least one variant of renal rickets, however, in which the biochemical features are sufficiently distinctive to warrant separate consideration at this time. This variant is known as the de Toni-Fanconi syndrome.

### *de Toni-Fanconi Syndrome*

The de Toni-Fanconi syndrome is a form of renal rickets with certain biochemical variations (hypophosphatemia, glycosuria, aminoaciduria). The syndrome occurs principally in consanguine children, but cases in adults have been recorded (McCune et al.). The bony lesions are those of rickets or osteomalacia in the adult, and of rickets, dwarfism and osteitis fibrosa prior to puberty. The biochemical changes are hypophosphatemia with normal levels of serum calcium, hyperchloremia, normoazotemia, hypophosphaturia, albuminuria, hyperaminoaciduria, particularly cystinuria,

with a normal blood level of amino acids, renal glycosuria, a lowering of blood bicarbonate, usually alkaline urine, and an excess of other organic acids in the urine including lactic acid and beta-hydroxybutyric acid. With the terminating renal insufficiency, hyperphosphatemia with low levels of calcium is likely to occur.

### *Pathogenesis*

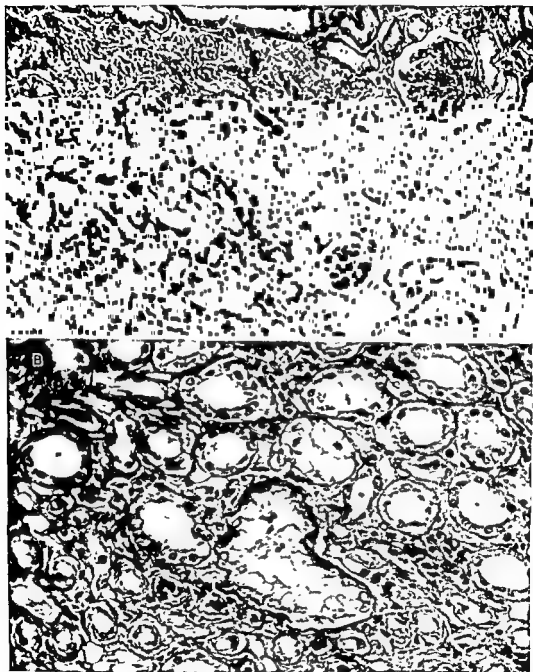
The explanations of this complicated physiologic derangement have been varied and at the present time, none is entirely satisfactory. It is not clear if the biochemical changes are the result or the cause of the renal changes. The possibility that the aminoaciduria itself produces renal damage is strengthened by the evidence of the deleterious effects on the kidney following the experimental administration not only of cystine (Cox et al.), but of other amino acids, including serine, lysine, arginine, histidine, aspartic acid and tryptophane. The other explanation offered is that the hyperaminoaciduria, glycosuria, and hyperphosphaturia are attributable to low renal thresholds, inasmuch as the blood levels of these substances are not elevated. Hottinger suggests that in some instances the reducing substance in the urine may be cysteine and may be mistaken for glucose. Fanconi believes that the aminoaciduria is caused by a faulty renal oxidative deamination. McCune suggests as a further possibility that the hyperphosphaturia may be the result of hyperparathyroidism.

### *Cystinosis, Cystinuria and the de Toni-Fanconi Syndrome*

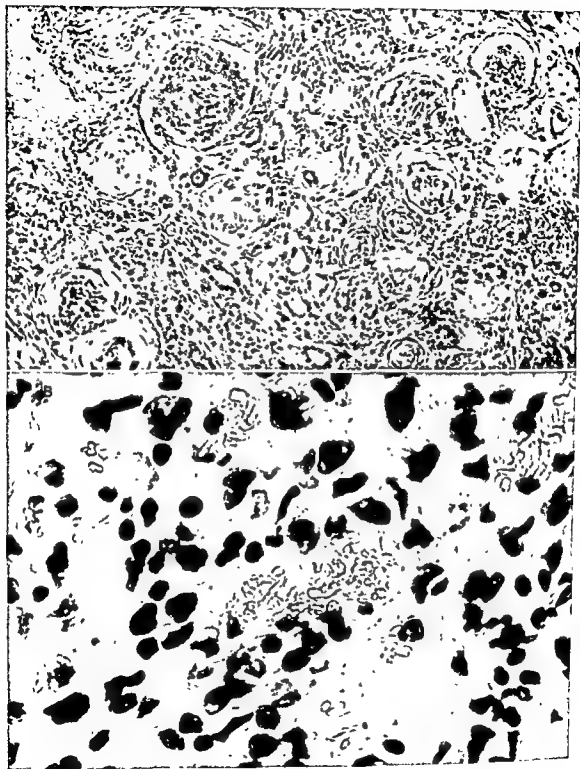
There appears to be a close relationship between the de Toni-Fanconi syndrome (with cystinuria) and the condition of hereditary cystinuria and cystinosis (deposits of crystals of cystine in various organs), although the relationship is not entirely clear. Cystinuria is one of the "inborn errors of metabolism" occurring as a familial trait in siblings. In young children, cystinuria, which in this age group is likely to be temporary and irregular, is commonly asso-

ciated with tissue cystinosis and rarely with cystine calculi; in older children, cystinuria tends to be associated with cystine calculi rather than with cystinosis. In these older children, therefore, the effects of the cystinosis are usually merely those of calculous pyelonephritis, if any at all (Freudentberg; Russell and Barrie). In the younger children, who are more prone to have cystinosis, the problem is often grave because of characteristically impaired resistance to infection and the likelihood of ultimate renal insufficiency. This age differential corresponds to the deleterious renal effects produced in young rats fed cystine in contrast to the lack of renal damage in older rats (Cox et al., Addis et al.).

No instance of the combination of cystinosis with glycosuria but without renal rickets has been recorded (McCune et al.). Three cases of cystinosis without renal rickets have been collected (McCune et al.), although most instances of cystinosis do have an associated renal rickets. In two of the above cases of noncalcic cystinosis, destruction of glomeruli, tubular atrophy and interstitial fibrosis were described. In two cases of cystinosis in siblings, illustrated in plate 206, the renal lesions appear to be a chronic glomerulonephritis, with severe tubular atrophy. In the third case, a six year old child, the kidneys show focal glomerular and tubular atrophy confined to no particular zone, and vacuolization in the loops of Henle (plate 205). The vacuolated epithelium did not take the stains for glycogen, although the pattern strongly suggested glycogenic vacuoles. The failure to stain positively may well have been on an artefactual basis in this instance. No vascular lesions were present and the focal atrophy of nephrons appeared too limited to have caused serious renal dysfunction. There is limited help to be derived from currently available data on the pathology of the kidney in the de Toni-Fanconi syndrome, or cystinosis, but it is apparent that the clinical entity may also occur when the changes are not histologically conspicuous.



FIGS A AND B. *De Toni Fanconi syndrome* (renal rickets, glycosuria, aminoaciduria, hypophosphatemia, etc.) The renal pathology has not been adequately clarified. In this instance of a child, aged 8, there was focal atrophy of individual nephrons, interstitial fibrosis, dense protein casts (figure A) and glycogen like vacuolization of the descending limbs and loops of Henle (figure B). No cystine crystals were present. (Histologic slides obtained through the courtesy of Dr. J. Gohman, Univ. of Louisville.)

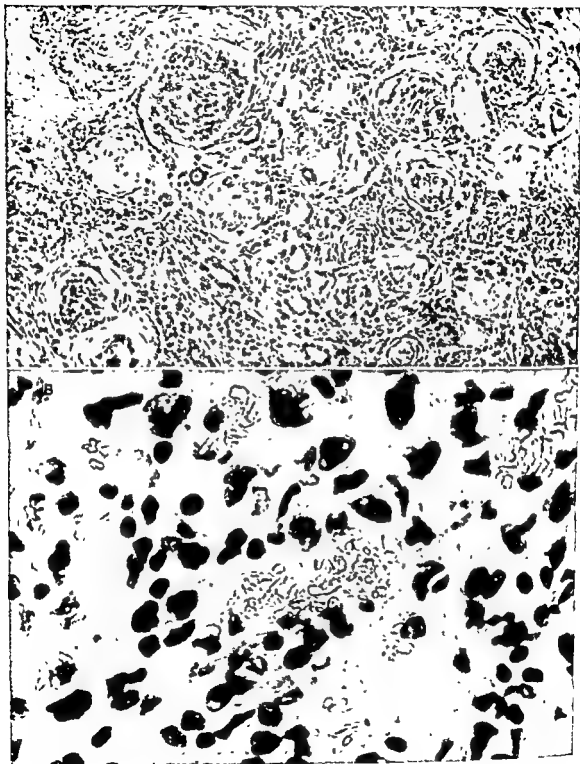


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FIG. A. Kidney from a case of cystinosis with intractable renal rickets in a 7 year old child showing various stages of glomerulitis, glomerular atrophy, and tubular atrophy, and marked sclerosis of afferent arterioles and interlobular arteries. Renal tubular and interstitial masses of cystine crystals were present and are illustrated in figure B. The crystals were present in insufficient numbers to be considered the cause of the renal changes which seem consistent with the diagnosis of chronic sclerosing glomerulonephritis. The patient had acidosis, hypophosphatemia and albuminuria with terminal hyperphosphatemia and uremia. No glycosuria was recorded. Cystine crystals were found in many organs, including lung, liver, adrenals, pancreas, thyroid, intestines, lymph nodes, spleen and testicle. A similar condition was found in a sibling. (Histologic slides obtained through the courtesy of Dr. Earl Clark.)



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FIG. A. Kidney from a case of cystinosis with intractable renal rickets in a 7-year-old child. It shows various stages of glomerulitis, glomerular atrophy, and tubular atrophy, and marked sclerosis of afferent arterioles and interlobular arteries. Renal tubular and interstitial masses of cystine crystals were present and are illustrated in figure B. The crystals were present in insignificant numbers to be considered the cause of the renal changes which seem consistent with the diagnosis of chronic sclerosing glomerulonephritis. The patient had acidosis, hypophosphatemia, and albuminuria with terminal hypophosphatemia and uremia. No glycosuria was recorded. Cystine crystals were found in many organs: mo'shing lung, liver, adrenals, pancreas, thyroid, intestines, lymph nodes, spleen, and testicle. A pinular evolution was found in a sibling. (Histologic slides obtained through the courtesy of B. Earl Clark.)



PLATE 206. CYSTINOSIS



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FIG. 1. A kidney from a case of cystinosis with intractable renal rickets in a 7 year old child showing various stages of glomerulitis, glomerular atrophy and tubular atrophy, and marked sclerosis of afferent arterioles and interlobular arteries. Renal tubular and interstitial masses of cystine crystals were present and are illustrated in figure 2. The crystals were present in insufficient numbers to be considered the cause of the renal changes which were consistent with the diagnosis of chronic sclerosing glomerulonephritis. The patient had acidosis, hypocalcemia and albuminuria with terminal hypophosphatemia and uremia. No glycosuria was recorded. Cystine crystals were found in many organs including lung, liver, adrenals, pancreas, thyroid, intestines, lymph nodes, spleen and testis. A similar condition was found in a still born (histologic slides obtained through the courtesy of H. Earl Clark).

# 13. Diseases of Vessels

## CLASSIFICATION OF VASCULAR DISEASES

### Capillaries

- Diabetic glomerulosclerosis
- Amyloidotic glomerulosclerosis
- Fat embolization

### Arterioles

- " " " "
- " " " "

### Arteries

- Arteriosclerosis
- Periarteritis nodosa
- Scleroderma
- Bacterial arteritis
- Thromboangitis obliterans
- Bilateral cortical necrosis
- Embolization and thrombosis

### Veins

- Thrombosis
- Thromboangitis obliterans

As will be indicated, it is possible for more than one of the above conditions to occur in the same kidney

### ARTERIAL (SENILE) NEPHROSCLEROSIS

The arteriosclerotic or senile contracted kidney is not of itself responsible for hypertension or renal insufficiency except in rare instances of unusual renal atrophy

#### Pathology

#### Gross appearance

The kidneys are about of normal size and are characterized by thickened capsules adherent particularly over wedge-shaped depressed atrophic scars. Such scarred areas correspond to the renal parenchyma that has undergone slow ischemic atrophy as a result of sclerosis and narrowing of the lumen of the large branches of the renal artery (plate 207)

#### Histologic appearance

Histologically, sclerosis involves the major arterial branches but may extend to the arcuate

arteries. In addition, there may be evidence of *ischemic atrophy* of the parenchyma particularly in the subcapsular regions. The foci of atrophy include lymphocytic infiltration about hyalinized fibrotic glomerular scars and atrophic tubules (plate 208). According to some observers, the scarred glomeruli may eventually disappear (Staemmler). Small cortical cysts, thought to be derived from Bowman's capsules, are frequently present. Areas of cortical atrophy, especially when accompanied by abundant lymphocytic infiltration, may resemble pyelonephritic scars. Naturally the arteriosclerotic kidney may be complicated by arteriosclerosis, pyelonephritis, embolization, thrombosis, amyloidosis and other conditions. Often the parenchyma may show practically no change, despite conspicuous arteriosclerosis.

Apart from the atrophic glomeruli in the scarred areas, scattered completely fibrotic glomeruli are usually found. "Axial" or intercapillary thickening of the glomeruli has been described as part of the senile kidney (Kimmelstiel). There appears to be ample histogenetic reason to believe that the mesangial thickening referred to is actually a *sclerosis of glomerular capillaries*. Moreover the association of this glomerulosclerosis—whatever its histogenesis—with the uncomplicated aging process cannot be confirmed. These glomerular tufts are indistinguishable from those glomeruli seen in hypertensive patients (McGregor), an observation convincingly documented by MacCallum.

Although the uncomplicated arteriosclerotic kidney presents no problem, as indicated, there may be superimposed on such a kidney any grade of arteriosclerosis with hypertension and renal insufficiency. Occasionally an eccentric sclerotic plaque partially occluding the ostium of a main renal artery appears to have been associated with and possibly responsible for the development of hypertension, presumably after the fashion of unilateral experimental occlusion of the renal artery in the rat. In isolated instances, the hypertension may be re-

lated to the abundant parenchymal atrophy that may occur in the kidney secondary to marked renal arteriosclerosis.

## ARTERIOLAR (BENIGN) NEPHROSCLEROSIS

### Introduction

*Benign nephrosclerosis* refers to the renal lesion observed in association with the clinical complex known as *essential, idiopathic, or benign hypertension*. Essential hypertension is predominantly a disease of the fifth, sixth, and seventh decades of life, although rare instances even in the teens are recorded. Most series indicate that the disease is somewhat more common in females (Weberby, Master et al.). Hypertension is rare among the Orientals, and apparently also among Negroes living in Africa. On the other hand, there appears to be a considerably higher incidence of essential hypertension among Negroes subjected to the competitive stress of an urban environment of the United States than among the white population in a similar situation. Similarly, the incidence of hypertension among the West Indian Negroes living in Panama is considerably greater than among the native Panamanians (Iberia). There seems to be a strong hereditary or, at least, familial element in essential hypertension. This, too, may be merely a reflection of environmental strain. The great majority of people with hypertension are said to fall into the atrophic constitutional habitus, with definite obesity an unquestionable added hazard.

### Clinical Aspects

The clinical picture of essential hypertension is variegated. The onset may be vague, and may be suggested by vasomotor and emotional instability characterized by blushing, sweating, fits of anger, irritation, excessive salivation, and sudden rises in blood pressure, that is, the *diencephalic syndrome* occurring in young women particularly (Page). Vertigo, tinnitus, insomnia, paresthesias, visual disturbances or pains in the extremities may be additional early symptoms. Frequently, evidence of cardiac insufficiency, such as anginal attacks, precordial oppression, dyspnea on exertion, or cardiac asthma, is the initial clue. In some instances, an actual apoplectic stroke may be the first indi-

cation of hypertension. Often, however, the first sign of hypertension is disclosed by the sphygmomanometer in a routine physical examination.

Generally, systolic pressures of 150 mm. and diastolic pressures of 90 mm. are considered the threshold of hypertension. Some insurance companies prefer to reduce their risk by adopting a lower standard of 140/80 for any age (Daley et al.). The old formula that the normal blood pressure for a given adult age may be computed by adding the age to 100 is no longer regarded as accurate (Robinson and Brucer, Robinson et al.). Pressures of 140/90 mm. Hg or greater occur in about 50 per cent of males and 60 per cent of females over the age of forty (Dell). With the lower limit of 150/90 mm. Hg, hypertension was found in the fifth decade in 25 per cent of men and 33 per cent of women, in the sixth decade, in 40 per cent of men and 50 per cent of women. Two-thirds of women past the sixth decade and the same number of men past the seventh decade had hypertension (Master et al.). These figures concern a somewhat selected sample of population, but they and other series indicate that nearly half the population over 50 years of age have hypertension according to the above definitions and the majority are without symptoms. About 80 per cent of people who die of hypertensive disease are over the age of 50. Moreover, about three-fourths of patients with hypertension die of some other disease (Dell).

When blood pressure fluctuates, there is some tendency to choose the lowest reading especially if it occurs under what are considered "relaxed conditions." However, such optimism appears unwarranted. It is becoming increasingly clear that individuals whose blood pressure reaches an abnormal level under any circumstances are predisposed to the subsequent development of frank hypertensive disease.

Pressures of 200 mm. systolic and 110 mm. diastolic are common in this disease. In association with the hypertension the patient may show evidence of cardiac hypertrophy and insufficiency, emphysema, coronary arteriosclerosis, hypertensive encephalopathy and in a small percentage of cases renal insufficiency. This last feature is to be stressed because, although the

pathologic changes of the kidney are emphasized in the study of essential hypertension, only about 7 per cent of the cases die in uremia.

### Prognosis

In essential hypertension attempts to correlate prognosis with the height of blood pressure are often not reliable. Although it is true that the level of hypertension and the complications therefrom in many cases vary with its duration, there are too many exceptions to warrant such a blanket rule. In a greater number of instances, the pressure may remain constant for years—10 to 15 or longer—and in others it rises slowly and in still others, rapidly. The elevated diastolic pressure is particularly important in estimating the gravity of prognosis. The mortality from cardiac failure or from clinically apparent vascular changes in other organs need have no direct relation to the height of the hypertension. On the other hand, Foa, Foa and Peet state that the determination of the ratio of the width of the wall to the size of the lumen (W/L) of arterioles in biopsy specimens of skeletal (intercostal) muscle is significant in determining the prognosis of patients with essential hypertension or hypertension secondary to chronic nephritis: the greater the ratio, the worse the prognosis, of course.

The early age of onset of the hypertension influences the prognosis adversely, hypertension initiated in middle age or later tends to progress more torpidly. Although essential hypertension occurs somewhat more frequently in women, its course is prone to be more severe in men. Diabetes mellitus after middle age seriously increases the likelihood of the development of hypertension. The reason for this predisposition has not been satisfactorily explained on any organic basis, but the suggestion has been made that the sclerosis of the efferent arteriole may play a role (Allen). The efferent arteriole is presumed to be constricted by angio-

tonin in experimental hypertension thereby raising intraglomerular tension; in the kidneys of hypertensives with diabetic glomerulosclerosis the efferent arteriole is often organically narrowed (plate 241E, F). As stated, obesity is a real hazard to hypertensive patients and, conversely, reduction in weight of such obese patients has been found to be followed by decrease in blood pressure (Walker; Freed; Levy et al.; Robinson et al.).

### Differential Diagnosis

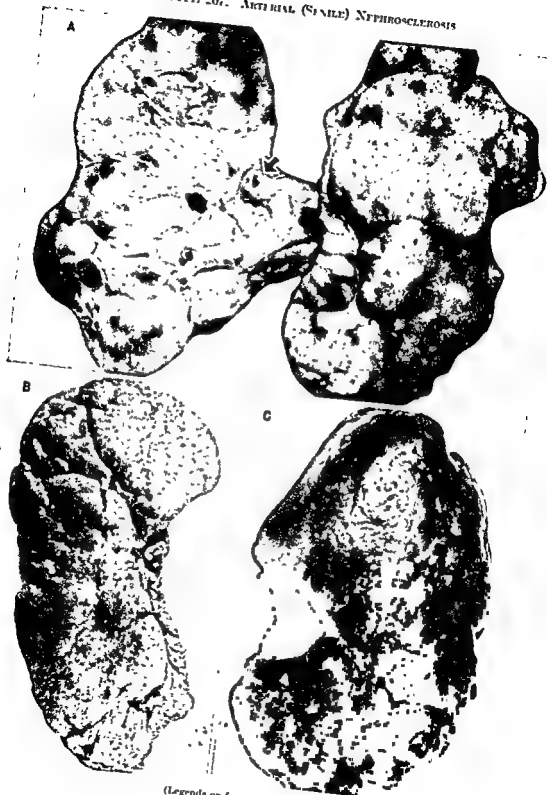
The picture of essential hypertension may be simulated by chronic glomerulonephritis, congenital polycystic kidneys, coarctation of the aorta, chronic pyelonephritis, pituitary basophilism, diencephalic lesions, adrenal hyperplasia, adrenal cortical adenoma or carcinoma, pheochromocytoma, renal amyloidosis, periarthritis nodosa, renal hypoplasia, neoplasms of the kidney, healed infarcts, gout nephritis and unilateral narrowing of the main renal artery by a sclerotic plaque, thrombus, or extrinsic mass. In these cases, as in essential hypertension, the diastolic as well as the systolic pressure is elevated. It is this criterion that categorically separates these conditions from aortic insufficiency, arteriosclerosis, hyperthyroidism, and heart block with bradycardia in which the diastolic pressure is not elevated despite the rise in systolic pressure.

### Urine

In most patients with essential hypertension there is no abnormal urinary finding. When abnormalities occur, they may be the result of cardiac rather than renal failure. In the former case, urinary volume diminishes but concentrating ability is not disturbed, in the latter, polyuria occurs as a compensatory attempt against the loss in concentrating power which for years may be associated with specific gravity no higher than 1.015. The failure to compensate for lack of concentration by increased

FIGS. A, B, AND C. Arterial nephrosclerosis characterized by sclerotic narrowing of the renal artery (arrow) and its main branches with resultant deep irregular parenchymal scars corresponding to infarcts.

PLATE 207. ARTERIAL (SIMILE) NEPHROSCLEROSIS



(Legends on facing page)

volume may mean cardiac impairment or dangerously progressive renal dysfunction. Nocturia occurs commonly in patients with essential hypertension either because the cardiac strain is eased at night, the circulation improved and urinary volume increased, or because, if function of the kidneys is impaired, the increased volume must be maintained even through the night to make up for diminished concentrating capacity.

*Albuminuria* may be present or absent in essential hypertension. When present it is usually slight in amount and is due to cardiac decompensation or to minor glomerular damage. Abundant albuminuria in an elderly patient with hypertension should lead to a suspicion of diabetic glomerulosclerosis, or, much more remotely, amyloidosis. Fishberg points out that the renal threshold for sugar may be elevated in essential hypertension so that the diagnosis of diabetes mellitus may be overlooked if complete reliance is placed on the absence of glycosuria.

The *sediment* may be entirely negative, or a few granular casts and leukocytes may be present. Isolated red blood cells in the urine may be the result of passive congestion of the kidney; if abundant, hematuria may indicate the malignant phase of the disease.

A low *filtration fraction* has been noted in early, moderately advanced and late stages of glomerulonephritis in contrast to the elevated filtration fraction of benign nephrosclerosis with hypertension (Cargill). The implication is that the increased filtration fraction in hypertension is caused by constriction of the efferent arteriole. Cargill observed, however, that as the vascular disease progressed, there was a decrease in the filtration fraction which he attributed to the progressive afferent arteriosclerosis counterbalancing the effect of efferent arteriole sclerosis.

### *Pathology of Arteriolar (Benign) Nephrosclerosis*

#### *Gross appearance*

The arteriosclerotic kidneys of benign nephrosclerosis vary in size depending on the duration and severity of the disease. Early the kidneys may be slightly larger than normal principally because of the congestion; in the late stage, they may shrink to less than half normal size. In Bell's series of 315 cases of benign nephrosclerosis from patients with essential hypertension, the combined weight of the kidneys was as shown in table 8. In other words, in about 21 per cent, there was no reduction in

TABLE 8—Combined Weight of Kidneys in Bell's cases\*

Combined Wt of Kidneys (Gm.)	% of 315 cases
60-99	1.6
100-199	28.9
200-299	43.6
300-399	18.4
400-475	2.5

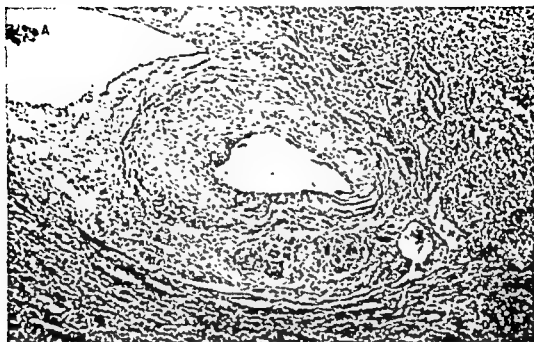
\* "Primary hypertension"

the size of the kidneys and in almost a third of the cases, there was marked contraction. There is no relationship between the weights of the kidneys and the heart.

In the initial stages, the surface may be smooth so that macroscopic findings may be deceptive (plate 209A). The surface very soon acquires a diffuse fine granularity that has been compared in appearance to scotch grain leather. In general, these kidneys have a purple-red hue so that they have been designated the "red" kidneys in contrast to the "white" kidneys of chronic glomerulonephritis (plate 67A). The purple-red color is produced essentially by the hyperemia particularly of the atrophic "troughs" separating the yellow-grey normal or hypertrophied tubules forming the elevated granules (plate 209B). The regularity of the

FIG. A Arteriosclerosis of arcuate artery in arterial nephrosclerosis, with associated parenchymal atrophy.

FIG. B Cortical depression and subcapsular cortical cyst common in arterial nephrosclerosis. In this case, arteriosclerosis of the afferent arterioles, as well as hypertension, were absent. In other words, even marked renal arteriosclerosis may occur with or without renal arteriosclerosis. Renal arteriosclerosis can only rarely be considered causally related to hypertension or renal insufficiency.



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volume may mean cardiac impairment or dangerously progressive renal dysfunction. Nocturia occurs commonly in patients with essential hypertension either because the cardiac strain is eased at night, the circulation improved and urinary volume increased, or because, if function of the kidneys is impaired, the increased volume must be maintained even through the night to make up for diminished concentrating capacity.

*Albuminuria* may be present or absent in essential hypertension. When present it is usually slight in amount and is due to cardiac decompensation or to minor glomerular damage. Abundant albuminuria in an elderly patient with hypertension should lead to a suspicion of diabetic glomerulosclerosis, or, much more remotely, amyloidosis. Fishberg points out that the renal threshold for sugar may be elevated in essential hypertension so that the diagnosis of diabetes mellitus may be overlooked if complete reliance is placed on the absence of glycosuria.

The *sediment* may be entirely negative, or a few granular casts and leukocytes may be present. Isolated red blood cells in the urine may be the result of passive congestion of the kidney, if abundant, hematuria may indicate the malignant phase of the disease.

A low *filtration fraction* has been noted in early, moderately advanced and late stages of glomerulonephritis in contrast to the elevated filtration fraction of benign nephrosclerosis with hypertension (Cargill). The implication is that the increased filtration fraction in hypertension is caused by constriction of the efferent arteriole. Cargill observed, however, that as the vascular disease progressed, there was a decrease in the filtration fraction which he attributed to the progressive afferent arteriosclerosis counterbalancing the effect of efferent arteriosclerosis.

### *Pathology of Arteriolar (Benign) Nephrosclerosis*

#### *Gross appearance*

The arteriosclerotic kidneys of benign nephrosclerosis vary in size depending on the duration and severity of the disease. Early the kidneys may be slightly larger than normal principally because of the congestion, in the late stage, they may shrink to less than half normal size. In Bell's series of 315 cases of benign nephrosclerosis from patients with essential hypertension, the combined weight of the kidneys was as shown in table 8. In other words, in about 21 per cent, there was no reduction in

TABLE 8—Combined Weight of Kidneys in Bell's cases\*

Combined Wt of Kidneys (Gm)	% of 315 cases
60-99	1.6
100-199	23.9
200-299	48.6
300-399	18.4
400-475	2.5

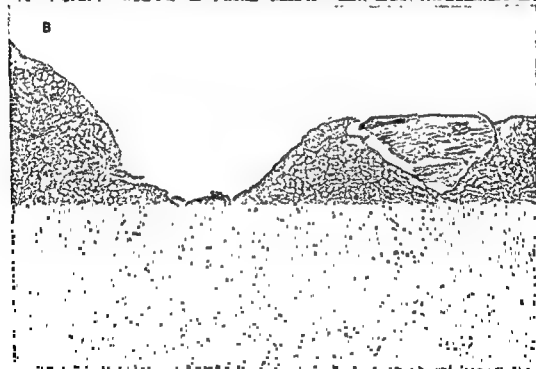
\* "Primary hypertension"

the size of the kidneys and in almost a third of the cases, there was marked contraction. There is no relationship between the weights of the kidneys and the heart.

In the initial stages, the surface may be smooth so that macroscopic findings may be deceptive (plate 209A). The surface very soon acquires a diffuse fine granularity that has been compared in appearance to scotch grain leather. In general, these kidneys have a purple-red hue so that they have been designated the "red" kidneys in contrast to the "white" kidneys of chronic glomerulonephritis (plate 67A). The purple-red color is produced essentially by the hyperemia particularly of the atrophic "troughs" separating the yellow-grey normal or hypertrophied tubules forming the elevated granules (plate 209B). The regularity of the

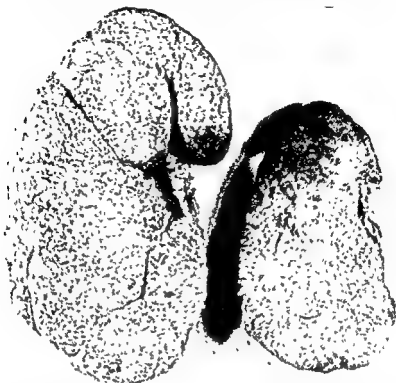
FIG. A. Arteriosclerosis of arcuate artery in arterial nephrosclerosis, with associated parenchymal atrophy.

FIG. B. Cortical depression and subcapsular cortical cyst common in arterial nephrosclerosis. In this case the cyst contained a small amount of fluid. In other cases the cysts were absent. In a few cases the cysts were filled with blood. In a few cases the cysts were filled with fibrin.



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A



B

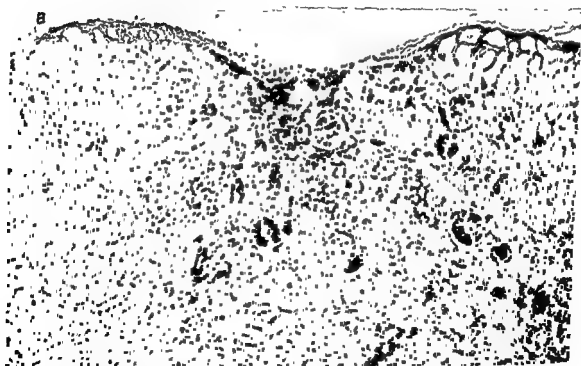


FIG. A. Kidneys of arteriolar or benign arteriosclerosis associated with hypertension and showing slight (left) and severe (right) degrees of contraction, along with the characteristic, fine granularity secondary to the sclerosis of afferent arterioles and interlobular arteries

FIG. B. Arteriolar (benign) nephrosclerosis associated with hypertension, illustrating the histologic picture of a typical surface granule characterized by crests of dilated tubules alternating with troughs of atrophic tissue. The sclerosis of interlobular arteries and afferent arterioles may be discerned (Elastica-van Gieson stain)

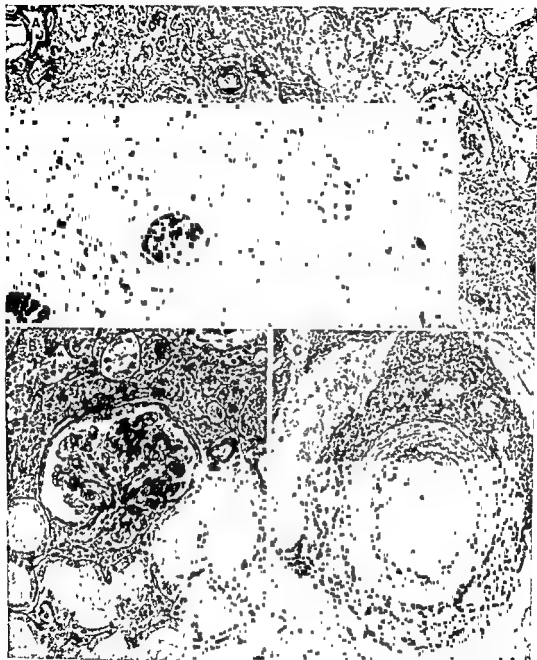
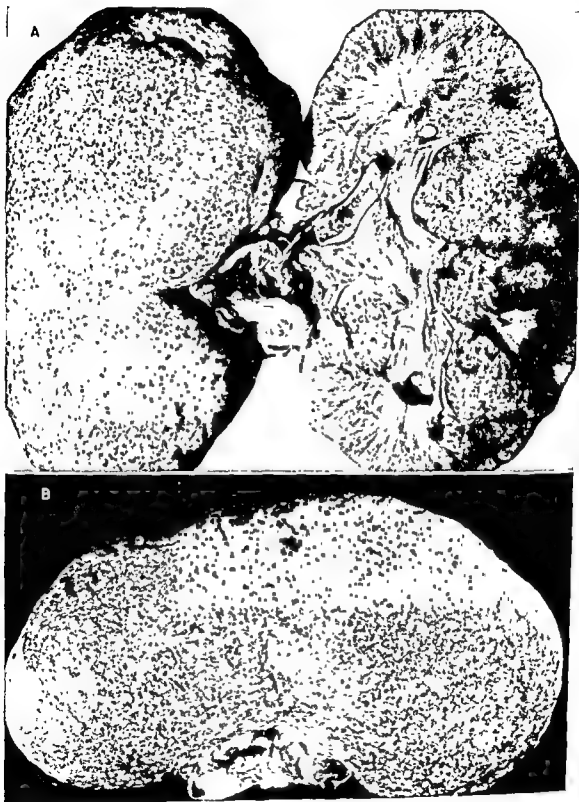


FIG. A Arteriolar nephrosclerosis showing atrophic and hyperplastic nephrons, scarred as well as essentially spared glomeruli, and sclerosis of afferent arterioles and interlobular arteries (Elastic-van Gieson stain)

FIG. B "Hypertensive glomerulus" of arteriolar nephrosclerosis consisting of sclerotic glomerulus with afferent arteriosclerosis. Portions of atrophic and hyperplastic nephrons are also included

FIG. C Hyperplastic sclerosis is often associated with the benign nephrosclerosis of hypertension and is characterized by reduplication of the internal elastic lamina. (Elastic-van Gieson stain)



ating a benign nephrosclerosis of much longer duration in (B). (A A F, I P Acc 4b, BU)

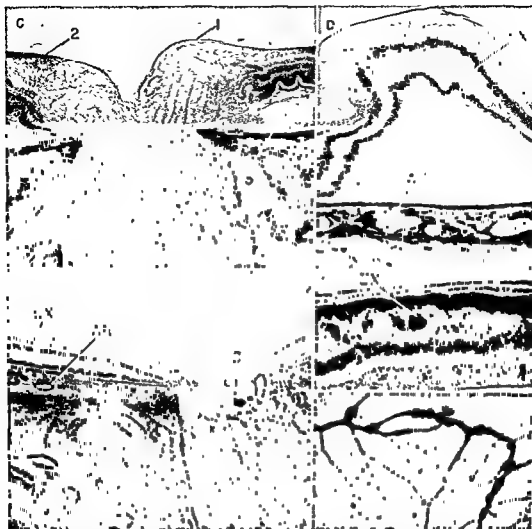


FIG C Hypertensive neuroretinopathy of malignant hypertension showing (1) papilledema, (2) retinal hemorrhage, and (3) subretinal exudate

FIG E Benign nephrosclerosis Hypertensive retinopathy with normal disc and nerve (D), exudate (Ex) ophthalmoscopically star shaped about macula and arteriosclerosis (Ar) of choroid

FIG D Hypertensive neuroretinopathy of malignant hypertension showing retinal detachment, retinal exudate (Ex), and arteriosclerosis of choroid (Ar)

FIGS F AND G Diabetic retinopathy with retinal exudate (Ex) in figure F, and arteriosclerotic segmental thickenings in figure G (Arch Ophth 44 539, 1950, Am J Ophth 32 457, 1949 )

(These photomicrographs were obtained through the courtesy of Dr David Weder, New York City)

mal lesions were found in fully 30 per cent of cases

*Objections to this latter study have been raised on the grounds that a small biopsy specimen of kidney might not be representative, since, it was declared, sclerosis of renal arterioles is segmented with intervening normal areas. The objection in this instance is not as serious as it might seem to be. Actually, afferent arteriosclerosis of hypertension spares very few nephrons and is sufficiently diffuse to be seen in almost any section in which the arteriole is present. What the findings of this biopsy material indicate is that hypertension may precede significant organic renal vascular change. This conclusion does not negate the possibility of functional renal arteriolar change antedating the hypertension. In any case, the fact still remains that with long-standing hypertension, one may anticipate diffuse afferent arteriosclerosis at postmortem. Furthermore, it is usually possible to estimate the degree of hypertension from the degree of arteriosclerosis observed in postmortem sections of the kidney. Moritz and Oldt state that in about 12 per cent of cases a minor degree of "arteriosclerosis" may occur in the absence of a history of hypertension. In our experience, diffuse afferent arteriosclerosis rarely occurs without associated hypertension. In general, the extent of the cardiac hypertrophy parallels the degree of afferent arteriosclerosis.*

*Juxtaglomerular Apparatus in Hypertension.* In connection with changes in the renal arterioles, mention should be made of the observations of the juxtaglomerular apparatus in hypertension. Detailed data about granularity, fibrillarity and hyperplasia have been published regarding these cells whose role is still ill defined. Their strategic location at the vascular pole of the glomerulus has led to the postulation that they exert control over the caliber of the afferent and efferent arterioles. The juxtaglomerular apparatus, however, is

normally variable in size and histology in different nephrons. Precise micrometric determinations in serial sections of a statistically significant sample of these cells in controlled and abnormal kidneys have not been done. Therefore conclusions regarding their hyperplasia and quality must be questioned.

*Tubules:* The tubules in the arteriosclerotic kidney show evidence of atrophy, hypertrophy and hyperplasia in much the same way as in chronic glomerulonephritis. In the latter, however, the compensatory changes of hypertrophy and hyperplasia are more marked. In addition there is considerably more blockage of the distal convoluted tubules by casts and consequently greater hydronephrotic distortion in the nephritic kidney. Lipid and hyaline droplet degeneration of the epithelium of the proximal convoluted tubules are common focal findings.

*Interstitium.* As portions of the nephron atrophy, there occurs a concomitant interstitial well vascularized, argyrophilic fibrous replacement associated with infiltrations of lymphocytes, plasma cells and histiocytes. This interstitial reaction occurs early as wedge-shaped areas between the surface granules and later involves other portions of the cortex.

### *Extrarenal Changes in Benign Nephrosclerosis* *Heart*

Although patients with hypertension are likely to have enlarged hearts, particularly with left ventricular hypertrophy, there is no direct correlation between the level of the blood pressure, the size of the kidneys, and the size of the heart. Remarkable surprises are occasionally encountered in the form of normal sized or only slightly enlarged hearts in patients with moderate, longstanding hypertension. As a rule however, hypertension of some duration and constancy is accompanied by cardiac enlargement. In those cases of hyperten-

FIG. A Small hemorrhagic infarct of accelerated (malignant) nephrosclerosis. The blood in the tubules illustrates one basis for the hematuria in malignant nephrosclerosis.

FIG. B Interstitial hemorrhage, necrotizing afferent arteriosclerosis and necrotizing glomerulitis of accelerated nephrosclerosis superimposed on benign arteriolar nephrosclerosis. The necrotizing glomerulitis is another mechanism for hematuria in malignant nephrosclerosis.

PLATE 213. ACCELERATED (MALIGNANT) NEPHROSCLEROSIS



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sion in which renal insufficiency develops, about 95 per cent of hearts weigh more than 400 Gm., and about 75 per cent weigh more than 500 Gm., in hypertensive women, the average weight of the heart is about 75 Gm. less than in males (Bell). There is no correlation between the level or duration of hypertension and the degree of coronary arteriosclerosis or coronary arteriolosclerosis. Whether or not the sclerosis of coronary vessels is caused by or is correlated with hypertension, nevertheless, it is often present in the age group afflicted with hypertension. Therefore, given two hearts with an equivalent degree of coronary arteriosclerosis, the one made larger by hypertension is obviously more likely to develop coronary insufficiency. The reason is, of course, that the myocardial muscle mass is more apt to outstrip its blood supply in the larger heart. In this same connection, it is to be noted that cardiac failure in essential hypertension may be precipitated by sudden additional cardiac stresses such as are produced by an abrupt rise in blood pressure, acute infections and possibly unusual exertion. Considerable medicolegal polemics have centered about the last mentioned factor without appreciable resolution of the problem.

### Brain

Patients with hypertension may develop signs and symptoms as a result of what has been termed *hypertensive encephalopathy*. These include transient palsies, pareses, aphasia and amaurosis as well as headache, vertigo, incoherence and even dementia. About 7 to 14 per cent of patients with hypertension develop fatal cerebral hemorrhage (Paullin et al.; Jane-way). Conversely it has been found that hypertension occurs in over 93 per cent of patients with massive cerebral hemorrhage not due to local causes such as trauma, aneurysm or neoplasms (Lippmann). Many of the evanescent symptoms are due to arterial and arteriolar sclerosis with areas of encephalomalacia or less marked foci of parenchymal degeneration.

### Eye

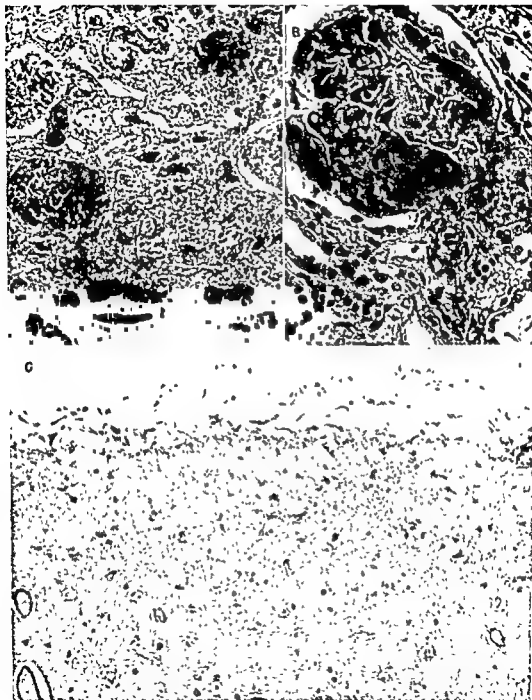
Fundal changes are common in essential hypertension, and are of great diagnostic and prognostic importance. Marked retinal arteriosclerosis and arteriolosclerosis, with tortuosity of the vessels, arteriovenous compression and "silver-wire" appearance, and "hard" white spots (vs. "cotton-wool" exudates) are the principal ophthalmoscopic findings in hypertension, and are absent, as a rule, in patients with merely generalized arteriosclerosis and normal blood pressure. The presence of retinal arteriosclerosis indicates that hypertension (of whatever etiology) has been present a considerable time, and is an unfavorable prognostic sign, except in patients with diabetes mellitus. In diabetes, this sign is not necessarily ominous. Arteriosclerotic retinopathy is not as grave a prognostic indication as is hypertensive neuroretinopathy, which it may closely simulate. The latter is characterized by papilledema, "cotton-wool" exudate, hemorrhages, and sclerosis of arteries and arterioles (plate 211C, D, E, F, G). Arteriosclerotic retinopathy or hypertensive neuroretinopathy may occur also in cases of chronic glomerulonephritis with hypertension.

### Lungs

Passive pulmonary congestion with hemoptysis, rarely of a severe degree, may occur with essential hypertension. Pulmonary emphysema is a common complication and, of course, adds to the myocardial strain.

### Endocrine glands

None of the endocrine glands shows a change that can be related to essential hypertension with the possible exception of the adrenal glands. It has been stated (Rinehart et al.) that the adrenal glands in hypertension weigh more than in a control group. This observation, which still lacks adequate statistical confirmation in view of Dempsey's data, has acquired



FIGS. A AND B *Malignant nephrosclerosis* with hemorrhagic infarction of glomeruli, hemorrhage in tubules, interstitium (A), and juxtaglomerular apparatus (B)

FIG. C *Hypertensive encephalopathy* was characterized in this instance by cerebral edema, and sclerosis of small arteries and arterioles

an added interest in view of Selye's emphasis on the role of the adrenal corticoids in the production of hypertension and nephrosclerosis. A comprehensive and critical review of the evidence for the relationship of the adrenal cortex to hypertension has been written by Sapeika.

## MALIGNANT NEPHROSCLEROSIS

### Introduction

The term "malignant nephrosclerosis" has been applied to the characteristic renal changes which reflect the clinical counterpart referred to as "malignant hypertension." The latter term was introduced by T. Fahr to designate a disease entity of fulminant hypertension and uremia. It is now clear that malignant hypertension and malignant nephrosclerosis do not represent a disease *suu generis* but rather a complication of one of several basic diseases that have hypertension as a common denominator. For example, the clinical, as well as the histologic, features of malignant hypertension may be superimposed not only on those of essential hypertension, but also on chronic glomerulonephritis, chronic pyelonephritis, pheochromocytoma, the Cushing syndrome of pituitary basophilism, adrenal cortical hyperplasia or neoplasia, and even amyloidosis. Rarely, the malignant nephrosclerosis develops so suddenly, and is so fulminant that it masks an underlying benign nephrosclerosis. There has been much discussion as to whether or not, as Goldblatt (1938) believes, renal failure, or some unknown humoral factor, must accompany the hypertension in order to produce the necrotizing arteritis of malignant hypertension. The evidence appears to be in favor of the theory that hypertension alone, particularly an elevated diastolic pressure (Fishberg) may cause the necrotizing vascular change (Wilson and Byrom). The observation of vascular necrosis in association with pheochromocytomas and with the experimental injection of adrenalin (Waters) is additional evidence for the latter point of view.

### Clinical Picture

Malignant hypertension is a complication that occurs in a somewhat younger age group than does the essential hypertension; it is found predominantly in the fourth, fifth, and sixth decades. Rarely, the typical clinical and pathologic picture of malignant hypertension is seen in children. The organs illustrated in plates 221 and 222 are from a child six years of age whose malignant nephrosclerosis was superimposed on a chronic glomerulonephritis. Another remarkable case, reported by Kennedy and Barker, was a seven year old girl with a malignant hypertension associated with unilateral chronic pyelonephritis. Her blood pressure was <sup>170-225</sup>/<sub>110-178</sub> and there was extensive hypertensive retinopathy.

The symptoms of malignant hypertension are those of rather abrupt onset of increased intracranial pressure as well as of renal insufficiency. The heightened intracranial pressure, simulating an intracranial tumor, may be manifested by nausea, vomiting, headache, stiffness of the neck, visual impairment, hypertensive neuroretinopathy with papilledema, retinal exudates and hemorrhages, convulsions and coma. The papilledema, which may reach 3 diopters, is a most reliable indication that the patient has progressed into the malignant phase of hypertension and may even precede the urinary changes such as albuminuria and hematuria. The papilledema may be unilateral for a time.

As stated, hypertensive neuroretinopathy is a most serious prognostic sign and, according to Fishberg, occurs in practically every case of malignant nephrosclerosis. Chasis and Goldring, however, disagree with Fishberg on this point, they found the neuroretinopathy absent in 23 per cent of 68 patients with malignant nephrosclerosis. Exophthalmus may also be present and is presumed to be due to the hypertensive encephalopathy. The spinal fluid pressure is usually elevated, occasionally to as high

as 500 mm of water. Most cases of malignant hypertension terminate in uremia.

The abrupt development of the phase of malignant hypertension is marked by gross, painless hematuria in about 20 per cent of cases and persistent microscopic hematuria in about 50 per cent (Goldring and Chasis). In some instances the glomeruli do not become focally necrotic and the hemorrhages come from altered arterioles within the renal interstitial tissue. In these cases the blood, exceptionally, may not reach the urine. Undoubtedly not all the hematuria is the direct mechanical result of necrosis of vessels or of glomeruli, but some is the consequence of the hemorrhagic diathesis commonly observed in uremic patients.

### *Pathology of Malignant Nephrosclerosis*

#### *Gross appearance*

The pathologic changes in the kidneys of patients with malignant hypertension obviously vary with the nature of the disease that preceded the malignant phase. In other words, as already indicated, the macroscopic features of malignant nephrosclerosis may be added to a kidney showing benign nephrosclerosis, chronic pyelonephritis, and even to kidneys from patients with a pheochromocytoma. Most often, however, the basic picture is that of a benign nephrosclerosis in which there has been little contraction (plate 211, 212A), occasionally the granulations are well marked. It is of interest that the kidneys of malignant nephrosclerosis are rarely very much shrunken, few weigh less than 120 Gm each. In other words, for reasons unknown, the very severity of the underlying benign vascular sclerosis may be responsible for sparing the kidney a superimposed malignant nephrosclerosis. The color of the kidneys with malignant nephrosclerosis is brownish or greyish red, the color commonly associated with "vascular" kidneys. The principal macroscopic feature that suggests the diagnosis are the "flea-bite" or punctate pin-head sized hemorrhages on the surface of a granular kidney.

#### *Histologic appearance*

Histologically, the essential changes are found especially in the interlobular arteries and the portions of the vascular tree distal to them. The arterial and arteriolar changes indicative of the malignant phase are these: (1) marked intimal thickening with increase in intimal fibroblasts, edema and lamination of intimal collagen, (2) fibrinoid necrosis of the vascular wall, and (3) the presence of red blood cells within the wall of the vessel (plates 215, 216).

The increased cellularity (fibroblasts as well as leukocytes), edema and lamination of the intima reflect an *acceleration* of the process of vascular sclerosis which, in benign nephrosclerosis, is characterized by a denser, more hyaline and less cellular intima. Karyorrhexis of the intimal fibroblasts and leukocytes is a common finding (plate 215A, B).

The fibrinoid necrosis may extend from the afferent arteriole directly into the glomerular capillaries so that foci of fused, granular, degenerated, smudgy, fibrinoid masses are often seen close to the hilum of the glomeruli (plate 214A, B). Thrombosis of small vessels is common (plate 218). The efferent arterioles, however, are spared (plate 218) in contrast to those of diabetic glomerulosclerosis. The afferent arteriosclerosis in amyloidosis, diabetic glomerulosclerosis, and benign nephrosclerosis generally has a smoother, more homogeneous, less granular quality than in malignant nephrosclerosis. Occasionally whole glomeruli appear to be infarcted (plates 213, 214). Not infrequently, some of the glomeruli show the proliferative changes of acute glomerulitis even with the formation of capsular crescents identical with those of subacute glomerulonephritis (plate 218A). These glomerular changes are ischemic in origin. The stroma of the cortex is often focally infiltrated with polymorphonuclear leukocytes. Stromal extravasations of blood, corresponding to the "flea-bite" hemorrhages observed grossly, are frequent findings. To repeat, additional histologic changes vary with the nature of the underlying renal disease.



FIG A Necrotizing afferent arteriolitis of accelerated nephrosclerosis characterized by smudgy fibrinoid alteration of the wall, endothelial swelling, karyorrhexis of fibroblasts and inflammatory cells, and narrowing of the lumen

FIG B Afferent arteriolitis of accelerated (malignant) nephrosclerosis with characteristically extreme narrowing of lumen, concentric increase of intimal fibroblasts, necrobiosis of inflammatory cells and fibrinoid necrosis

FIG C Typical lamination, intimal cellularity, and luminal narrowing of accelerated afferent arteriosclerosis. This picture even without the necrosis indicates the accelerated hypertension

FIG D Hemorrhage within walls of necrotic afferent arterioles

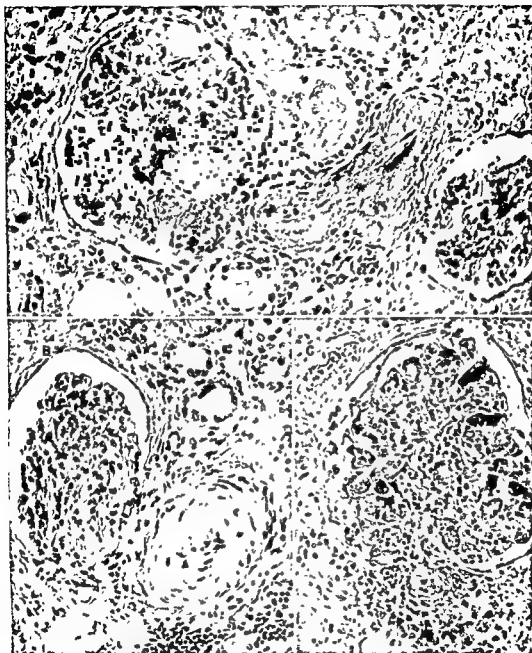


FIG A Necrotizing afferent arteriolitis and glomerulitis of accelerated (malignant) nephrosclerosis. The glomerular hyalinization must be differentiated particularly from diabetic glomerulosclerosis and endocarditic glomerulonephritis

FIG B Variant of afferent arteriosclerosis with marked edematous narrowing of lumen but without fibrinoid necrosis in accelerated nephrosclerosis

FIG C Glomerulitis of accelerated nephrosclerosis showing numerous thrombi in glomerular capillaries. This lesion is not to be confused with that of disseminated lupus erythematosus. Necrotizing arteriolitis is also present

PLATE 217. ACCELERATED (MALIGNANT) NEPHROSCLEROSIS



FIG. A Typical smudgy fibrinoid swelling with extreme narrowing of lumen of afferent arteriole in accelerated nephrosclerosis. The associated proliferative glomerulitis is secondary to the ischemia. This patient was a 34 year old white man with a blood pressure of  $\frac{180-230}{90-120}$  (A F I P. Acc 106542)

FIG. C Dilatation of necrotic afferent arteriole is common in accelerated nephrosclerosis and has been thought to reflect increased intraglomerular tension

FIG. B Fibrinoid necrosis and contescence of capillary loops of glomerular tuft in accelerated nephrosclerosis

FIG. D Capillary thrombi and mild fibrinoid necrosis of capillaries constitute one of the less striking glomerular changes of accelerated nephrosclerosis. This change also occurs in acute glomerulonephritis

present prior to the superimposition of the malignant phase.

Alterations may occur in organs other than the kidney in cases of malignant nephrosclerosis. The vessels of the retina are practically always involved in hypertensive retinopathy. Arteriolar necrosis may be found in the testis, pancreas, adrenal gland, gallbladder and liver. In some of these organs, for example the pancreas, a characteristic parenchymal atrophy may occur (Schurmann and MacMahon). Of course, in view of the frequency with which patients with malignant nephrosclerosis develop uremia, the extrarenal changes, previously described in the section on Uremia, may also be found in such patients.

### *Pathogenesis*

The prominent position of hypertension in the list of leading causes of death has prompted a great expenditure of effort in search of the cause of this disease. This effort received enormous impetus with the discovery by Goldblatt and his associates (1934) of a relatively simple and constantly effective method for the experimental production of hypertension by means of constriction of the renal arteries with silver clamps. During the next decade, and especially the first half of that decade, the natural ramifications of the problem were explored, a few modifications of the experimental methods were introduced, and several new concepts of the pathogenesis of hypertension were added. To date, no single concept is entirely adequate, no satisfactory therapeutic agent or procedure is available.

Many theories have been proposed to explain the pathogenesis of hypertension. The common occurrence of renal arterial and arteriolar sclerosis has strongly suggested that renal ischemia is a main pathogenetic factor. Some investigators blame excess of circulating pressor substances, insufficiency of antipressor hormones, the adrenal glands, the pituitary gland, diet especially with high protein, purine or sodium

components, obesity, psychogenic stress, or abnormality of a vasomotor center.

Clearly, many of the hypotheses built about these general headings are simply complementary facets of an over-all mechanism. For example, a concept of neural genesis of hypertension need not preclude humoral, endocrinologic contributions; similarly, the notion that renal ischemia or renal vasoconstriction is responsible for hypertension does not necessarily imply that no other broad accessory factors are set into operation.

### *Conclusions from experimental data*

An examination of the experimental facts indicates that the following are pertinent phenomena with regard to the production of hypertension:

1 Hypertension, both systolic and diastolic, sustained for years, can be produced in dogs by constriction of both main renal arteries, the silver clamps of Goldblatt are generally used for this purpose. This hypertension need not be accompanied by renal dysfunction.

2 Transient hypertension is produced in most dogs if the clamp is applied to only one main renal artery, chronic hypertension occurs in some dogs and in other animals such as rats, sheep and goats with constriction of one main renal artery. Sustained hypertension may be produced in most dogs by clamping one main renal artery, provided the contralateral kidney is removed as if this kidney, left intact, neutralized the pressor substance released by its vasoconstricted fellow. Sustained hypertension may be produced also by clamping the aorta proximal but not distal to the origin of the renal arteries, clamping of the celiac axis, the superior or inferior mesenteric arteries, the splenic or femoral arteries does not yield hypertension.

3 Release of the vasoconstricting clamp is followed by a return of the blood pressure to normal levels in a matter of hours.

4 Simultaneous occlusion of the main renal veins along with the constriction of the arteries does not result in hypertension. Moreover, oc-



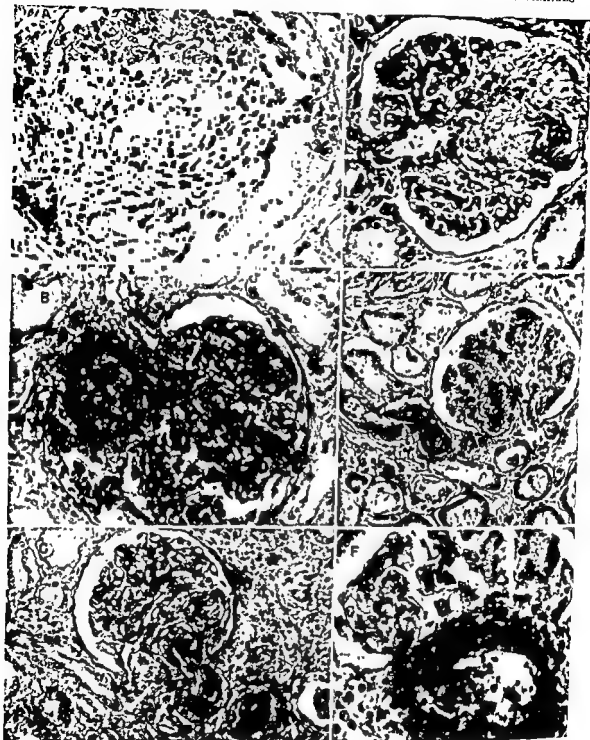


FIG A Proliferative glomerulitis of accelerated nephrosclerosis provoked by ischemia and simulating the changes of glomerulonephritis

FIG B Glomerulus of accelerated nephrosclerosis showing marked necrosis of afferent arteriole with no change in efferent arteriole

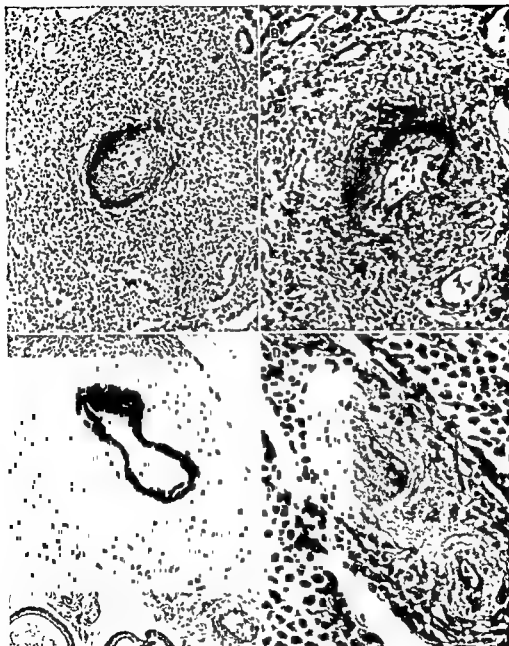
FIG C Accelerated nephrosclerosis with necrotizing arteriolitis and organically negative efferent arteriole

FIG D Glomerulus showing fibrinoid necrosis of accelerated nephrosclerosis and torpid glomerular fibrosis of benign nephrosclerosis.

FIG E Accelerated nephrosclerosis with necrotizing afferent arteriolitis and no change in the efferent arteriole.

FIG F Necrotizing afferent arteriolitis with marked dilatation

PLATE 219. ACCELERATED (MALIGNANT) NEPHROSCLEROSIS



FIGS. A AND B. Necrotizing arteritis (interlobular) of kidney of periarthritis nodosa, to be differentiated from arteritis of accelerated nephrosclerosis. The abundant inflammatory reaction in these instances is strong presumptive evidence in favor of periarthritis or mycotic arteritis versus the arteritis of malignant nephrosclerosis. Rarely do renal arteries exhibit such inflammatory response as a result of malignant hypertension.

FIGS. C AND D. Necrotizing arteritis of testis of rat following severe hypertension produced by cellophane perinephritis.

PLATE 220. GLOMERULONEPHRITIS WITH ACCELERATED  
(MALIGNANT) NEPHROSCLEROSIS



FIG A Subacute glomerulonephritis with necrotizing afferent arteriolitis in a patient with the clinical picture of accelerated (malignant) nephrosclerosis. Even though found with subacute glomerulonephritis, this arteriolitis is an indication of severe hypertension.

FIG B Chronic sclerosing glomerulonephritis with superimposed accelerated (malignant) nephrosclerosis. The laminated, markedly narrowed sections of artery represent a histologic indication of severe hypertension. In other words, the accelerated (malignant) phase may complicate glomerulonephritis as well as benign nephrosclerosis and other conditions associated with an elevated blood pressure.

PLATE 221 ACCELERATED (MALIGNANT) NEPHROSCLEROSIS SUPERIMPOSED  
ON GLOMERULONEPHRITIS

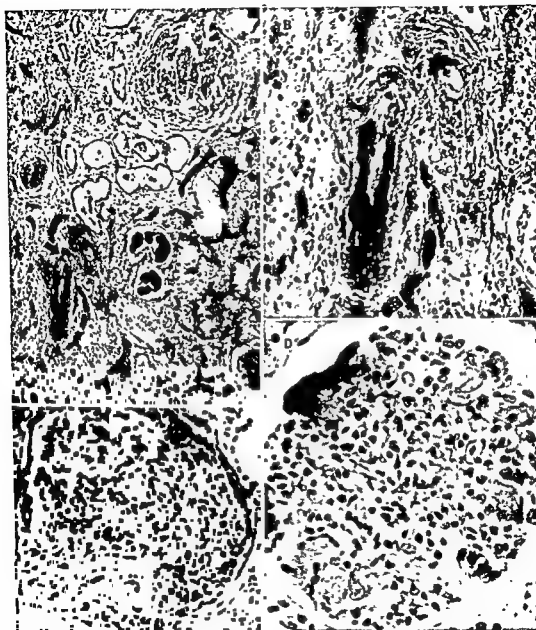


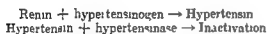
FIG A Chronic sclerosing glomerulonephritis with clinically and histologically superimposed accelerated nephrosclerosis

FIG C Necrotizing afferent arteriolitis of chronic glomerulonephritis with superimposed clinical and histologic accelerated nephrosclerosis

FIG B Higher magnification of necrotizing interlobular arteritis pictured in figure A

FIG D Acute exudative glomerulonephritis with thrombosis simulating accelerated (malignant) nephrosclerosis This glomerular lesion is not of itself indicative of hypertension

clusion of the renal veins after hypertension has been produced by clamping of the renal artery is followed by reduction of the pressure to normal (Goldblatt, 1947). The indication of this experiment is that constriction of the renal artery causes the release of a pressor substance to the general circulation and that this substance is withheld from the general circulation by closing the renal vein. Injection of blood from the renal vein of an explanted kidney with a constricted artery into a normal animal results in hypertension, as if the pressor substance were humoral. To some observers, the pressor agents are vasoconstricting amines which lead to hypertension in patients whose kidneys fail to deaminate them (Bing and Zucker). Most investigators believe the pressor substance to be *angiotonin* or *hypertensin*. This material is the product of *renin* (apparently a proteolytic enzyme liberated by the kidney) plus *renin* substrate, or *hypertensinogen* (a pseudoglobulin) (Houssay and Taquini). The tissue protein that destroys *angiotonin* or *hypertensin* is known as *hypertensinase* or *angiotonase* (Braun-Menéndez et al.), that is:



5 Hypertensive effects similar to those obtained by constricting the main renal arteries may be obtained by enveloping the kidneys in cellophane, silk, a fish-skin envelope, tantalum foil or gauze impregnated with collodion, usually, but not in all cases, with the production of a constricting perinephritis.

6 Occlusion of a ureter and constriction of the ipsilateral main renal artery of a dog do not

result in even transient significant elevation of blood pressure. This is to say that an altogether functionless kidney on one side does not cause hypertension.

7 In animals in which hypertension has been produced by constriction of the main renal arteries, the blood pressure which may fall after a while, may be restored to hypertensive levels by further tightening of the arterial clamps. The fall in blood pressure in these instances is attributed to the development of collateral circulation through the capsule and pedicle. Use of this principle by means of splenorenomy has been made in lowering blood pressures of dogs made hypertensive by constriction of the main renal arteries (Cerqua and Samaan). Separation of the kidney from the spleen results in restoration of the hypertension. Splenorenomy in man does not effect a reduction of hypertension, a discrepancy which suggests to Victor that the mechanisms producing hypertension are different for man and dog.

8 Excessive constriction of both main renal arteries, or of one main renal artery along with *contralateral nephrectomy* or *contralateral ureteral occlusion*, results in uremia and malignant hypertension with necrotizing arteriolitis and arteritis in organs other than the kidneys (plate 219C, D). Similar results are obtained with cellophane perinephritis.

9. Contrary to initial data, hypertension results from bilateral nephrectomy in dogs sustained with artificial kidneys (Grollman et al.). This experiment suggests to Grollman that the hypertension results not from a substance which the kidney secretes to the general circu-

FIG A Chronic membranous glomerulonephritis from a 5 year old with associated malignant hyper

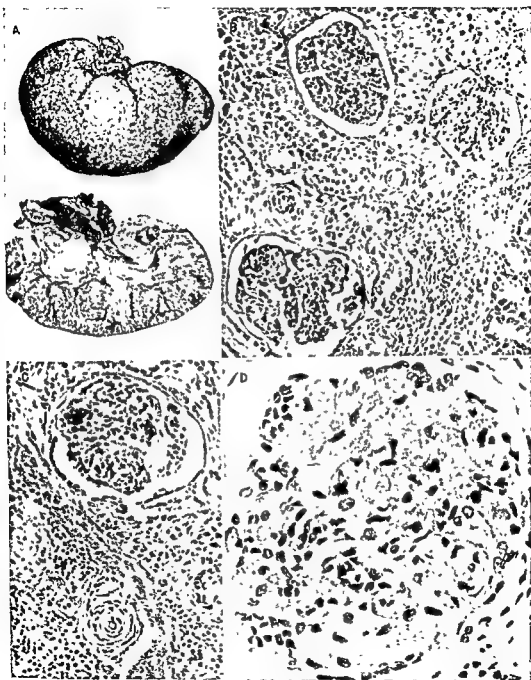
nephrosclerosis. The patient initially had the nephrotic syndrome.

FIG C Chronic membranous glomerulonephritis from kidney of figure A. The cellular, fibrillar interlobular artery reflects the acceleration of malignant nephrosclerosis.

FIG B Chronic membranous glomerulonephritis with acceleration. Section taken from kidney illustrated in figure A. The glomerular change is of the combination lobular and membranous type.

FIG D Glomerulus of malignant nephrosclerosis with fibrinoid necrosis of its capillaries, taken from kidney of figure A. The few intact capillary walls show thickening of the membranous type associated with the nephrotic complex.

PLATE 222 CHRONIC MEMBRANOUS GLOMERULONEPHRITIS WITH SUPERIMPOSED  
MALIGNANT NEPHROSCLEROSIS IN A CHILD



(Legends on facing page )

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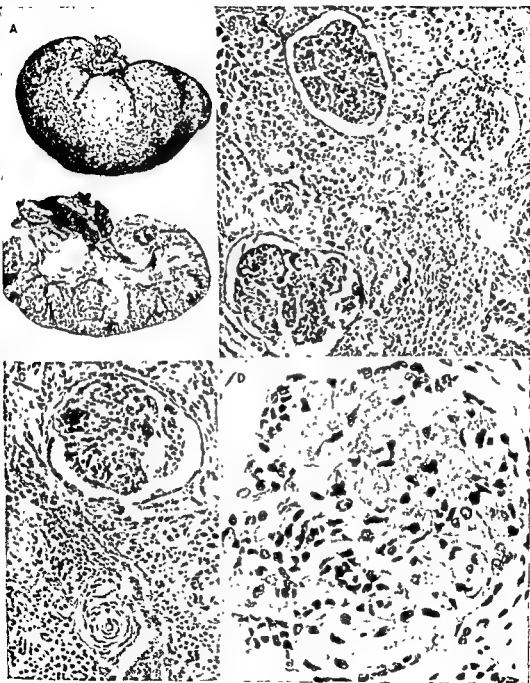
FIG A Chronic membranous glomerulonephritis from a 6 year old with associated malignant hypertension. The surface granularity and scattered petechiae give these kidneys a remarkable picture identical with that of the adult kidneys with malignant nephrosclerosis. The patient initially had the nephrotic syndrome.

FIG C Chronic membranous glomerulonephritis from kidney of figure A. The cellular, fibrillar interlobular artery reflects the acceleration of malignant nephrosclerosis.

FIG B Chronic membranous glomerulonephritis with acceleration. Section taken from kidney illustrated in figure A. The glomerular change is of the combination lobular and membranous type.

FIG D. Glomerulus of malignant nephrosclerosis with fibrinoid necrosis of its capillaries, taken from kidney of figure A. The few intact capillary walls show thickening of the membranous type associated with the nephrotic complex.

PLATE 222. CHRONIC MEMBRANOUS GLOMERULONEPHRITIS WITH SUPERIMPOSED  
MALIGNANT NEPHROSCLEROSIS IN A CHILD



(Legends on facing page)



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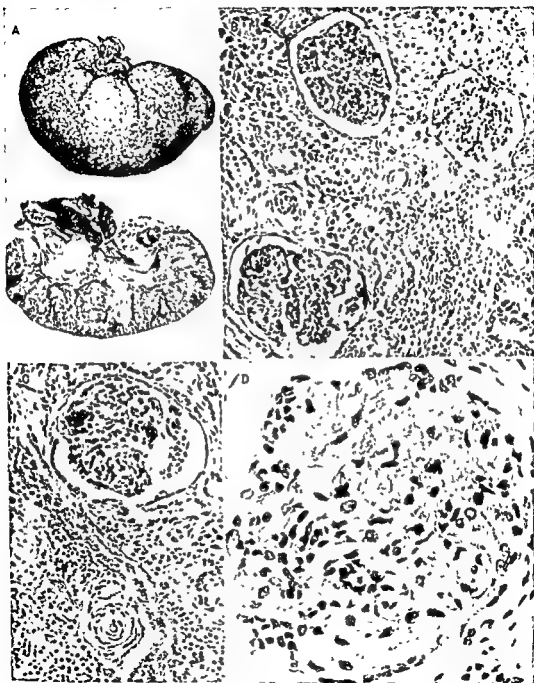
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FIG B Chronic membranous glomerulonephritis with acceleration. Section taken from kidney illustrated in figure A. The glomerular change is of the combination lobular and membranous type.

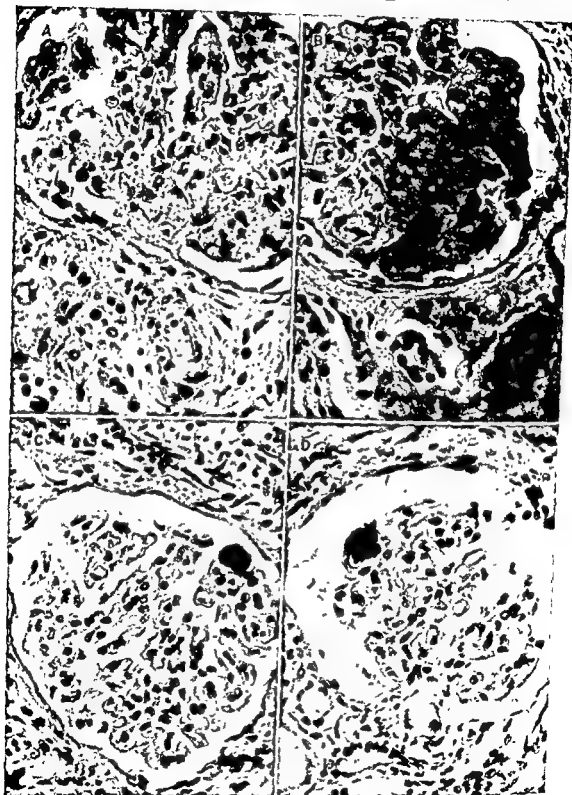
FIG D Glomerulus of malignant nephrosclerosis with fibrinoid necrosis of its capillaries, taken from kidney of figure A. The few intact capillary walls show thickening of the membranous type associated with the nephrotic complex.

PLATE 222. CHRONIC MEMBRANOUS GLOMERULONEPHRITIS WITH SUPERIMPOSED  
MALIGNANT NEPHROSCLEROSIS IN A CHILD



(Legends on facing page )

PLATE 223. CHRONIC MEMBRANOUS GLOMERULONEPHRITIS AND SUPERIMPOSED  
MALIGNANT NEPHROSCLEROSIS



FIGS A AND B Chronic nephrotic glomerulonephritis with superimposed accelerated or malignant nephrosclerosis; the accelerated phase is demonstrated by the partially necrotic afferent arterioles (arrow) and glomeruli (From kidney illustrated in figure A, plate 222)

FIGS C AND D. Chronic membranous nephrotic glomerulonephritis with hypertension and focal "wire-loop" necrosis of isolated capillaries

PLATE 234. HYPERTENSION: UNILATERAL CHRONIC PYELONEPHRITIS WITH  
SUPERIMPOSED ACCELERATED (MALIGNANT) NEPHROSCLEROSIS



FIG. A. *Markedly atrophic pyelonephritic kidney* removed surgically from a hypertensive patient with unilateral disease. The lower kidney from another patient is included for contrast.

FIG. B. *Tubular dilatation, protein casts and interstitial fibrosis* from atrophic kidney of figure A.

FIG. C. *Necrotizing arteriolitis* (arrow) of malignant hypertension (from pyelonephritic kidney of figure A).

lation but from the failure of the kidney to act on a substance normally in the circulation.

10 The adrenal cortex is necessary for the development of hypertension

11. There are conflicting data on the vascular changes in the unobstructed kidney of rats in which malignant hypertension has been produced by constriction of the main renal artery of the opposite kidney. According to Wilson and Byrom necrotizing arteriolitis develops in the kidney with the free renal artery because of intense vasospasm associated with increased intrarenal vascular pressure whereas in the opposite, clamped kidney, the vessels are normal as if protected by the obstruction within the more proximal main artery. Goldblatt (1947) is inclined to attribute the arteriolitis to accompanying renal insufficiency or possibly to spontaneous lesions antedating the experiment. Goldblatt's opinion that renal insufficiency is required for the production of necrotizing arteriolitis of malignant hypertension is a point of view not universally shared (e.g., Page, Fishberg).

12 As in human hypertension, viscosity and volume of blood, cardiac rate and output, venous and circulation times play no part in experimental hypertension

13 Constriction of the artery to the kidney explanted to the groin or neck also results in hypertension so that an intact nerve supply is not essential for this phenomenon.

14. Sustained reduction in renal blood flow is not a constant prerequisite for the development of hypertension in dogs or humans, although such reduction in animals is the rule, as it is in cases of hypertension in humans when uremia is present. Reduction in blood flow is

not accompanied by abnormal arteriovenous difference in oxygen. Constriction of the main renal artery also produces a diminished renal pulse pressure which many observers consider significant in the mechanism of hypertension.

15. Arteriosclerosis of the kidney is not produced as a result of experimental hypertension.

The absence of renal insufficiency or of more than minimal arteriolosclerosis in 50 per cent of biopsy specimens of the kidney in cases of hypertension can not be used convincingly as nullifying evidence against the concept of the renal origin of hypertension even if it does indicate that renal arteriolosclerosis is not essential. This is especially the case if it is believed with Grollman that the hypertension occurs because the kidney fails to produce its normal supply of a humoral agent. It is trite but relevant to remark that dysfunction of an organ need not necessarily be accompanied by histologic change. The alternate theories of the renal origin of hypertension are that the kidney elaborates an excess of circulating pressor substance, or that the kidney fails to detoxify normally existing pressor compounds, such as pressor amines (Bing and Zucker) because of the insufficiency of oxidative deamination of amino acids. To Grollman, however, these generally accepted "pressor-antipressor" theories are irreconcilable with the fact that hypertension persists in the absence of renal tissue and that, therefore, the hypertension could not be caused by renal pressor substances

#### *Unilateral Renal Disease and Hypertension*

The occurrence of hypertension in patients with unilateral renal disease has been offered as additional evidence of the renal origin of hypertension in humans. Such data must be tem-

FIGS A AND C. Cortical necrosis of the kidney (figure A). Although supplied by normal main renal artery shown below in figure C, the histologic sections (plate 226) reveal evidence also of malignant nephrosclerosis. The opposite kidney and renal artery are shown in figures B and D.

FIGS B AND D. Normal contralateral kidney (figure B), despite the markedly sclerotic, recently thrombosed, main renal artery, shown below in figure D. The histologic sections are illustrated in plate 226. The patient was a 52 year old man.

These kidneys are from a case of hypertension with a superimposed malignant phase, and a terminal stage of the disease with the thrombosed renal artery but of the one with the kidney with the occluded vessel only" (Arch. Path. 51: 30-37, 1951).

PLATE 225 HYPERTENSION (UNILATERAL RENAL DISEASE): OCCLUSION OF RENAL  
ARTERY WITH CONTRALATERAL CORTICAL NECROSIS AND CONTRALATERAL  
ARTERIOLOSCLEROSIS



(Legends on facing page )

pered, however, with the fact that the blood pressure may be temporarily lowered quite non-specifically by a variety of operations not associated with the kidneys (Volini and Flaxman). Furthermore, in several large series of cases, the incidence was as high or higher in the control population as in those patients with unilateral renal disease: 22.8 per cent and 21.8 per cent respectively (Friedman, Moschkowitz and Marrus), 24 per cent and 27.5 per cent (Oppenheimer, Klemperer and Moschkowitz); 20.3 per cent and 29.0 per cent (Baggenstoss and Barker).

There are individual cases, nevertheless, in which the total evaluation of the evidence compels a pathogenetic linkage of the hypertensive state with the unilateral renal disease. The particularly impressive features of these cases are the occurrence of severe hypertension in infants or children, the presence of arteriosclerosis in only one of the kidneys in some instances, and, above all, the sustained relief of hypertension following nephrectomy. These are factors that supersede the sphere of the statistical studies just cited. Examples are two of Butler's patients, aged 7 and 10 each, with unilateral chronic pyelonephritis and relief of hypertension after nephrectomy. The period of followup was limited in the report to 20 months and 3 months respectively. Another case is the 7 year old girl mentioned previously, whose hypertension of  $\frac{170-225}{110-178}$  was reduced to normal levels within several months after removal of a pyelonephritic kidney, the hypertensive retinopathy also disappeared. The pressure has remained normal for at least five years, at the time of the last report (Kennedy and Barker). Another is a 5 year old boy with an ectopic

pelvic kidney and a blood pressure of 155/105. After nephrectomy, the blood pressure remained within essentially normal limits for the following ten years.\* At the end of 12 years of observation, his blood pressure was 132/80 and there was no evidence of cardiac enlargement (Burkland et al.). Gasul, Glasser and Grossman added nine cases from the literature to one of their own, the ages varying from 2½ to 12 years, in which the hypertension was relieved for at least a year after nephrectomy. Eight of these were examples of chronic pyelonephritis; one was a hydronephrotic and the last was an "ectopic" kidney.

Another remarkable case, illustrated in plates 225 and 226, was characterized by marked arteriosclerosis of the main renal artery with terminal thrombosis; the opposite renal artery was widely patent and without necrosis. The parenchymal vessels of the kidney with the sclerotic main renal artery were essentially normal, while those of the contralateral kidney with the patent main renal artery showed sclerosis of the arcuate, interlobar and afferent arterioles, characteristic of benign and malignant hypertension (Aronson and Sampson). A terminal cortical necrosis developed in this kidney, the parenchyma of the kidney with the thrombosed, sclerotic main renal artery was spared. Other instances have been reported of occlusion of one main renal artery with little or

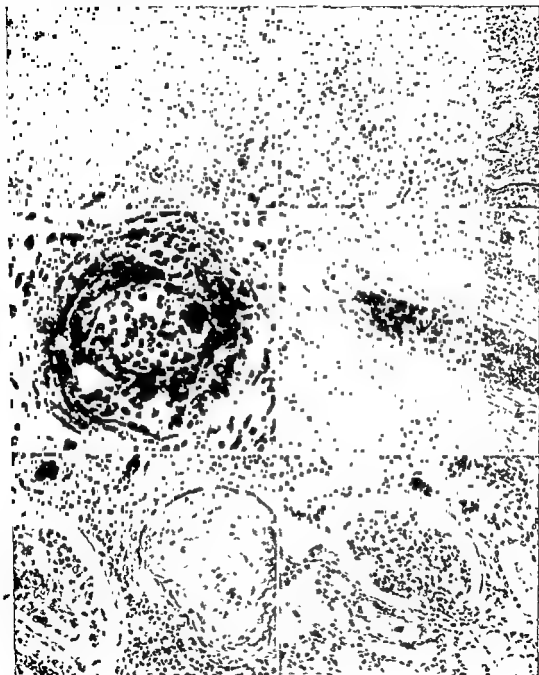
FIGS. A, B, AND C Sections from the necrotic kidney of figure A, plate 225, showing the marked hyperplastic sclerosis of small arteries and arterioles (figures A and C), and the necrosis of an interlobular artery (figure B), indicating an associated malignant nephrosclerosis. The reason for the susceptibility of this one kidney to cortical necrosis is probably the pre-existing parenchymal sclerosis which made the kidney particularly vulnerable to a reduction in blood pressure. Thrombosis of the contralateral renal artery may have precipitated the altered hemodynamics by a reflex, or other neurogenic mechanism.

\* The authors of this report (Burkland et al.) believe the main renal artery of the ectopic kidney was partially occluded by a "smooth muscle plug" with an elastic lamina. Actually, this "occlusion" appears to represent a well-known artefact produced by invagination of the wall of the artery (plate 333). This artefact, however, in no way invalidates the essential thesis of the report.

FIGS. D, E AND F The parenchyma of the grossly normal kidney of figure B, plate 225, shows no significant histologic change despite the sclerosis and

effects of the hypertension. That this presumption does not always obtain is illustrated in plate 227.

PLATE 226. HYPERTENSION: OCCLUSION OF RENAL ARTERY WITH CONTRALATERAL  
CORTICAL NECROSIS AND CONTRALATERAL ARTERIOLOSCLEROSIS



(Legends on facing page.)



PLATE 227. HYPERTENSION IN UNILATERAL RENAL DISEASE: UNILATERAL  
THROMBOSIS OF RENAL ARTERY WITH IPSOLATERAL ATROPHY  
AND ARTERIOLOSCLEROSIS

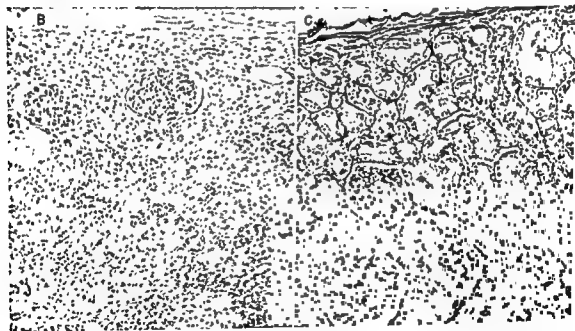
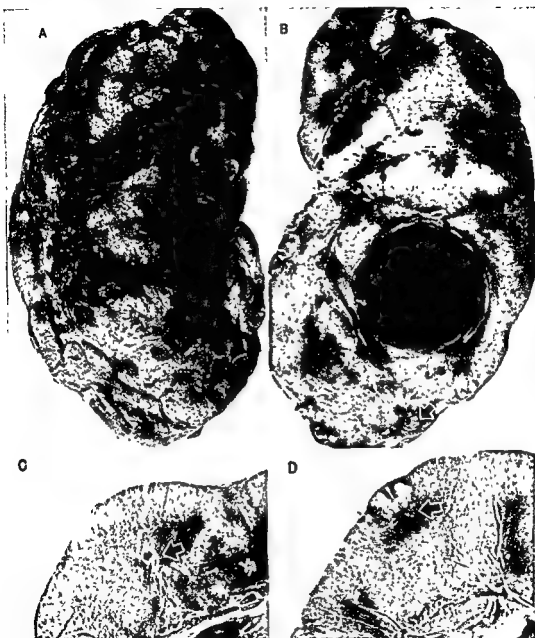


FIG A Organized thrombus of left renal artery with moderate atrophy of left kidney and associated hypertension The right kidney is of normal size and its artery is of normal caliber

FIG B Section from left kidney shown in figure A, showing evidence of tubular atrophy Arteriosclerosis is present in contrast to the opposite kidney (C).

FIG C Section from right kidney in above figure A, showing an essentially normal histologic picture, including an absence of arteriosclerosis The usual result in cases of unilateral occlusion of the renal artery is arteriosclerosis of the contralateral kidney as in the case illustrated in plates 225 and 226



FIGS A AND B Kidney with *periarthritis nodosa* showing irregularly scarred capsular surface corresponding to ischemia produced by involvement of various sized arteries. One of these arteries is aneurysmal in proportions and is filled with thrombus, others, such as the arcuate arteries (arrow) are extremely thickened and have narrowed lumens.

FIG C *Periarthritis nodosa*. An involved thrombosed arcuate artery is seen (arrow).

FIG D Small renal infarct and appertaining thrombosed arcuate artery are shown (arrow).

no changes in the parenchyma of the appertaining kidney, but with malignant nephrosclerosis in the opposite kidney of which the main renal artery was normal (Saphir and Ballenger, Schwartz and Gross)

There are definite exceptions to the rule that when the main renal artery is compromised, arteriosclerosis occurs only in the contralateral, originally normal kidney. In the case shown in plate 225, the atrophic kidney with arteriosclerosis is on the side of the occluded main renal artery, in the opposite kidney, the vessels are normal. Hypertension was present. In instances of unilateral parenchymal disease, as, for example, chronic pyelonephritis, the abnormal kidney is not protected from the occurrence of arteriosclerosis. This feature is illustrated in plate 224C in which malignant nephrosclerosis is shown superimposed on unilateral chronic pyelonephritis with marked renal atrophy.

#### *Unilateral nephrectomy for hypertension*

In hypertensive cases with unilateral renal disease, either of the main renal artery or parenchyma, or both, the contralateral kidney is observed at autopsy to be altered usually by the vascular changes of benign nephrosclerosis, and occasionally, even of malignant nephrosclerosis. Many of the failures to relieve hypertension by unilateral nephrectomy of an abnormal kidney are very likely based on the presence of arteriosclerosis produced in the opposite initially normal kidney by the hypertensive state. In such instances, an earlier nephrectomy might have preceded the development of contralateral renal arteriosclerosis which appears to sustain the hypertension after nephrectomy. If the hypertension in a given case can reasonably be attributed to unilateral renal disease, it is clear that relief from nephrectomy cannot be anticipated unless the hypertension is discovered early. The exact definition of "early" is impossible to construct, but some idea of its range is derived from Braasch's observation that less than 1 per cent of patients with hypertension apparently secondary to unilateral renal disease are amenable to therapy for hypertension by nephrectomy. Moreover, it must be borne in mind that the hypertensive state may

occasionally be made worse by nephrectomy, depending particularly on the state of the retained kidney.

#### *Summary*

In summary, it would seem that most of the facts best fit a concept of the renal role in the genesis or mediation of essential hypertension. As indicated previously, it would be dogmatically hazardous, and probably wrong, to dismiss the contributing factors of constitution, environmental stress, diet, endocrines, particularly the adrenal glands, and an inherent or acquired vulnerability of a vasomotor center or vascular bed to humoral stimuli.

### PERIARTERITIS NODOSA

#### *Introduction*

Kuśmaul and Maier are credited with the first description of periarteritis nodosa in a patient clinically suspected of having trichinosis. This report was published in 1866 and the clinical and pathologic (muscle biopsy) differentiation from trichinosis is often as much of a problem now as it was then. The pathogenetic role of hypersensitivity developed during the course of a prolonged infection was stressed by Gruber, convincingly reaffirmed by Spiegel, and subsequently effectively investigated by Rich with particular emphasis on the effects of the sulfonamides. The hypersensitive (hyperergic, allergic) concept of the nature of periarteritis nodosa is now generally accepted. Supporting evidence for the allergic hypothesis from human material is derived from the eosinophilia in the peripheral blood and in the local lesions, the fibrinoid alteration in the vessels, and the common association with asthma and glomerulonephritis (Spiegel). Because of the increased opportunity for sensitization on account of the use of antibiotics, vaccines and sera in wholesale quantities, it is believed that the incidence of periarteritis nodosa has increased considerably in recent years.

#### *Clinical Symptoms*

The discordant array of signs and symptoms in itself is one of the characteristic features of periarteritis nodosa. This is the natural result of the number of organs involved by this usu-

PLATE 229. PERIARTERITIS NODOSA

A

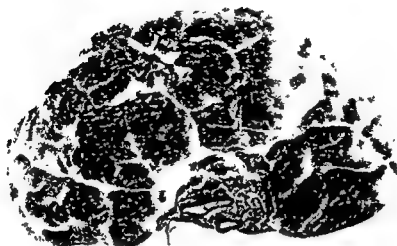
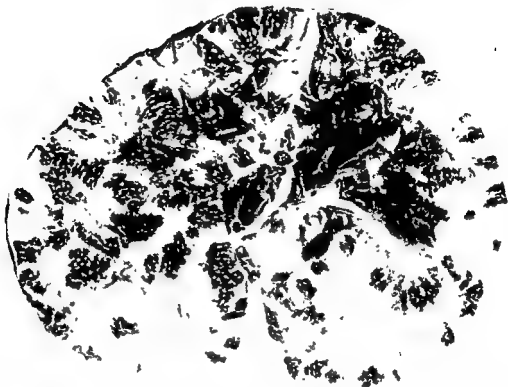


FIG A Striking surface lobulation in periarthritis nodosa due to diffuse involvement of renal arteries

FIG B Periarthritis nodosa of kidney showing thrombosis, aneurysmal dilatation and marked narrowing of arcuate artery by granulation tissue

PLATE 230. PERIARTERITIS NODOSA

A



B

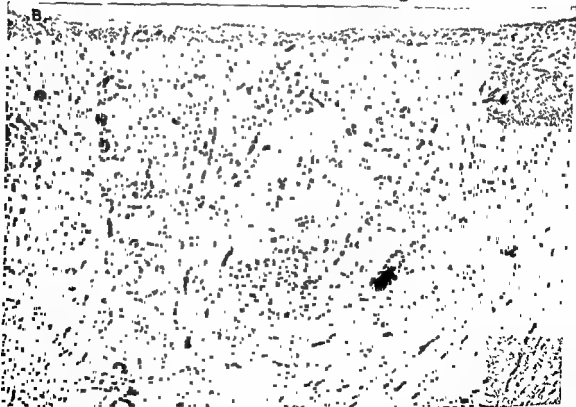


FIG. A Multiple infarcts due to periarteritis nodosa involving main branches of renal arteries and arcuate arteries. Thus extensive degree of infarction produces a gross picture similar to that of bilateral cortical necrosis.

FIG. B Cortical infarct and thrombosis of interlobular artery in periarteritis nodosa.

ally diffuse vascular disease. The process, however, selects certain organs above others and therefore symptoms pertaining to these structures predominate. Polyneuritis, polymyositis, gastrointestinal symptoms, and evidence of renal damage are particularly common. In addition, signs of sepsis, acute cholecystitis, hepatic infarcts, acute pancreatitis, myocardial infarction, erythema, purpura, or subcutaneous nodules, serositis and severe hemorrhage may be present. Eosinophilia is often observed, and may reach a level of 79 per cent (Strong).

### *Renal Involvement*

The kidney is the most commonly involved organ in cases of periarteritis nodosa (74 per cent, Gruber, 80 per cent, Arkim). The clinical evidence of renal involvement includes mild, moderate or malignant hypertension (17 of 30 cases, Ralston), renal insufficiency (33 per cent of cases, Ralston and Koale), hematuria, on occasion severe enough to cause death (Spiegel), perirenal mass (hematoma), and pain in the renal area. An attempt to diagnose periarteritis nodosa by Addison counts has been reported by Krupp, who finds the sediment characteristic of all the stages of glomerulonephritis telescoped into one composite aggregate (page 172). This sediment, he states, is quite similar to that found in the urine in disseminated lupus erythematosus, notwithstanding their histologic differences. Inasmuch as these Addison counts are from a diversity of types of cases (periarteritis nodosa, disseminated lupus erythematosus) with at least an equal diversity of pathologic changes, it is difficult to understand the mechanism of the similar urinary sediments.

### *Pathology*

#### *Gross appearance*

The kidneys with periarteritis nodosa may appear quite normal grossly. When gross changes appear, they vary with the stage, extent and complications of the disease. In the acute phase, the surfaces of the kidney may be mottled with hemorrhagic and yellow areas. In later stages, highly irregular pittings and depressions from infarcts or areas of ischemic atrophy occur (plates 228, 229). In other words

the kidneys may show the picture of malignant nephrosclerosis, acute glomerulonephritis, renal and perirenal hematomas, sometimes massive, and infarcts of different ages. Renal infarcts were present in 35 of Gruber's 63 cases. The infarcts may be so extensive as to simulate a complete cortical necrosis (plate 230 A). Usually the diagnosis is suggested by the examination of the vessels in the sectioned surface of the kidney. The cross sections of the arcuate arteries especially may be abnormally prominent, thickened and thrombosed, and the corresponding parenchyma may show the evidence of the ischemia (plate 230). Or, aneurysmal dilatation and thrombosis of even larger vessels, for example, the interlobar arteries, may be found. Rupture of arteries (plate 228) may lead to massive intrarenal hemorrhage or perirenal hematomas. In addition, the kidneys in periarteritis nodosa may show evidence of benign or malignant nephrosclerosis, or acute diffuse glomerulonephritis.

### *Histologic appearance*

*Acute Stage.* The lesions of periarteritis nodosa may be acute, healed, or recurrent. Veins are rarely involved. The acute stage is characterized by brightly acidophilic focal or massive fibrinoid degeneration of the arterial wall involving any or all of the coats and associated with little or with abundant inflammatory reaction (plate 229B, 231). The fibrinoid degeneration is stated to begin in the media, but it may begin in any portion of the vascular wall. The initial localization is said to be dependent on the size of the vessel, but even in vessels of the same size, particularly of the arcuate arteries, the initial site of fibrinoid alteration may vary. Often included in the area of fibrinoid necrosis are the elastic laminae, particularly the internal elastic lamina, and a portion of the media. These structures are frequently disrupted as if by an extremely virulent, rapidly effected reaction so that the tough laminae may be torn into several fragments and displaced outward toward the adventitia. This disruption, which is clearly shown in the Weigert's elastica-van Gieson stain, weakens the wall and is responsible for the subsequent aneurysmal dilatation (plate 232).

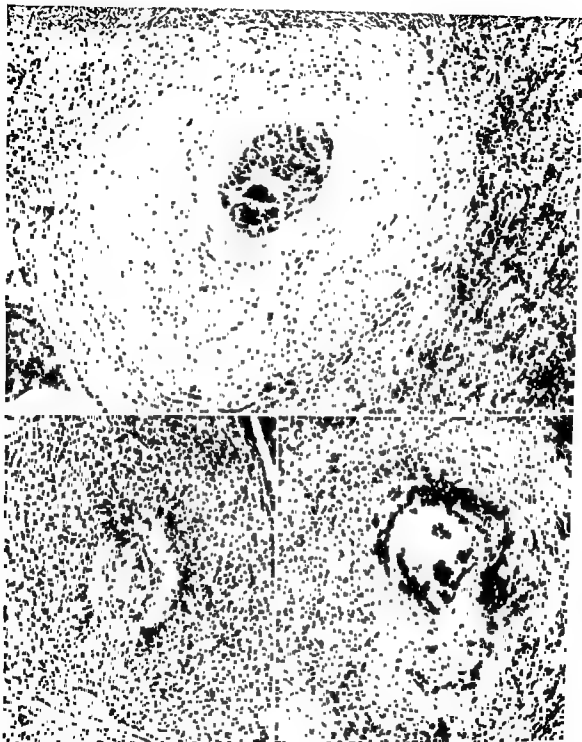


FIG A *Periarteritis of arcuate artery with acute and chronic involvement of all coats of the vessel including the periadventitial tissue*

FIG B *Fulminant exudative inflammation and fibrinoid degeneration in periarteritis nodosa*

FIG C. *Periarteritis nodosa with smudgy fibrinoid degeneration and inflammatory reaction.*



FIG A *Periarteritis nodosa* (arcuate artery) showing intimal sclerosis, disruption of the elastic lamina and aneurysmal dilatation responsible for the nodosity (Elastica-van Gieson stain)

FIG B *Disruption of elastica* and marked intimal sclerosis with extreme luminal narrowing of arcuate artery in "healed" *periarteritis nodosa* (Elastica-van Gieson stain)



The panarteritic inflammatory response typically consists of an abundant, diffusely distributed collection of eosinophilic leukocytes, polymorphonuclear leukocytes, lymphocytes, plasma cells and histiocytes. In the past, the presence of eosinophilic leukocytes has been regarded as one of the essentials for the diagnosis of periarteritis nodosa. This criterion has proved too rigid although it was perhaps justified at the time because of the then current tendency to include extraneous forms of arteritis in this group. In point of fact, periarteritis nodosa in the acute stage need not be characterized by eosinophilic leukocytes. Thrombosis and periadventitial hemorrhage occur frequently at this stage. In addition to the haphazard outpouring of inflammatory cells, the acute stage may appear as granulomas with giant cells forming a conspicuous element of the response. This latter reaction was known before the use of the sulfonamides, but is now commonly related to their use.

*Healed Stage* The acute exudative and alterative stage may progress to the healing stage in individual vessels. Rarely only the healing or healed residue of acute periarteritis nodosa is found; usually some focus of acute arteritis is present along with the healed vessels. The intima and media become eccentrically thickened by banal, at first cellular and well-vascularized, then densely sclerotic granulation tissue with marked encroachment on the lumen of the vessel (plate 232). The granulation tissue may extend in nodular formation beyond the adventitia. With longer survival, the cellular, vascularized granulation tissue becomes indifferently dense and relatively acellular. Old foci of residual hemosiderin-filled macrophages in the media, adventitia or even in the periadventitial region may indicate the nature of the ashes, especially if elastic tissue stains still reveal a torn lamina. As a matter of practical diagnostic clue, the mere presence of a minute eccentrically placed lumen in marked disproportion to the width of the wall of an intrarenal artery is strongly suggestive of an old process of periarteritis nodosa. Combine these with a dense sclerosis of the wall, spots of hemosiderin, and disrupted laminae and the diagnosis can hardly be anything else with the possible exception of

a bacterial arteritis. The impression is gained that, very much as in the case of acute exacerbation of chronic glomerulonephritis, in which fibrotic glomeruli may occasionally undergo fibrinoid degeneration (plate 82), so also in healed periarteritis nodosa, a scarred vessel may succumb to an acute fibrinoid exacerbation (plate 231C).

So much for the primary vascular change of periarteritis nodosa. The acute diffuse glomerulonephritis that often accompanies periarteritis nodosa may be exudative, proliferative, or necrotizing, and is best regarded as a pathogenetically related, rather than a coincidental change of periarteritis nodosa. It occurred in one-third of Gruber's 63 cases, and in 3 of Spiegel's 17 cases. Arterial involvement need not be present in the kidneys with glomerulonephritis in patients with periarteritis nodosa, as witness the case of Helpern and Trubek. Secondary or superimposed changes may include those of malignant nephrosclerosis, infarcts in various stages and of various sizes, and a form of tubular alteration that characterizes the atrophy produced by slowly progressive ischemia of renal vessels about the caliber of the arcuate arteries. This change is marked principally by moderate separation of the tubules by the increased interstitial fibrous tissue, and by a conversion of the cells of the proximal tubules, which come to resemble the epithelium of distal convoluted tubules (plate 234, 235). The cells lose their brush border and their acidophilic cytoplasmic granules, and become diminished in height. The glomeruli participate in the atrophy to a lesser degree.

#### *Differential Diagnosis*

The differential histologic diagnosis of periarteritis nodosa includes mycotic (bacterial or rickettsial) arteritis, the arteritis of malignant nephrosclerosis, the arteritis of disseminated lupus erythematosus, giant cell arteritis, and thromboangiitis obliterans. It may be impossible to differentiate a given vascular lesion, out of setting, in any of the above diseases from periarteritis nodosa. Several associated features may be of help. These diagnostic clues are the demonstration of infecting organisms in a case of mycotic arteritis, the glomerular wire-loop

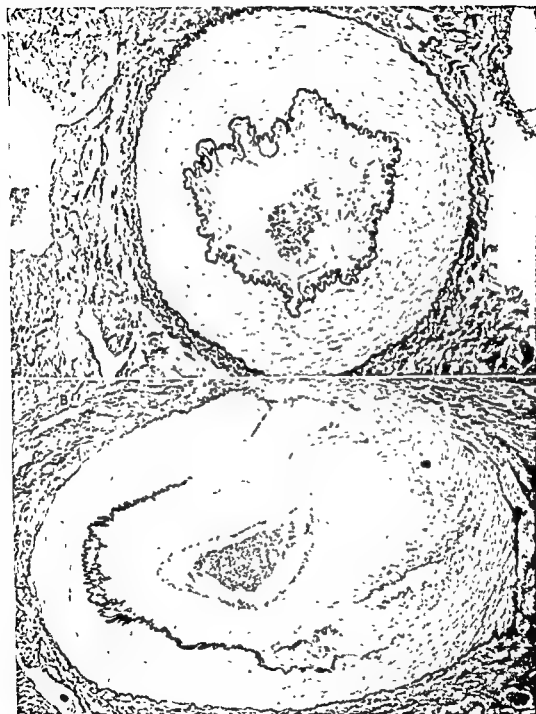


FIG. A Essentially normal arcuate artery with elastic-van Gieson stain, in contrast to the vessels of periarteritis nodosa illustrated in plate 232

FIG. B "Disruption" of elastic lamina in hyperplastic sclerosis without periarteritis nodosa. No residual vascularized granulation tissue of periarteritis nodosa is present (elastic-van Gieson stain). Actually, the process in this section is not one of disruption, but of a loss of affinity for the stain. The reduplicated elastic lamina can still be made out faintly.

PLATE 234. PERIARTERITIS NODOSA



FIG A *Slow ischemic atrophy of proximal tubules due to narrowing of arteries in periarthritis nodosa. The glomeruli are spared. The large segment of diffuse atrophy on the left is in contrast to the normal proximal tubules on the right. The proximal tubules are the most sensitive to ischemic atrophy.*

FIG B *Diffuse chronic ischemic atrophy, principally of the proximal tubules in periarthritis nodosa. The glomeruli are relatively spared, rarely, focal endocarditic glomerulonephritis occurs.*

lesions of lupus erythematosus, and the characteristic evidence of accelerated arteriosclerosis and arteriolosclerosis of malignant hypertension, particularly in the smaller arteries and arterioles as against the usually larger ones of periarteritis nodosa. In addition, in periarteritis nodosa, one looks for the absence of venous involvement, and, of course, the stigmata of periarteritis nodosa, especially the nodular healed lesions with minute lumens, organized thrombi, disrupted elastica, and hemosiderotic macrophages. It should be emphasized again that diffuse visceral arteritis has, in the past, been taught to be the expected finding in disseminated lupus erythematosus and rickettsial diseases. Nevertheless, as a matter of quantitative fact, it is uncommon in the kidneys of disseminated lupus erythematosus, and occurs infrequently and very sparsely in the kidneys of even epidemic and tick-borne typhus, it is practically never seen in scrub typhus. If the appendix is excluded, periarteritis nodosa is uncommonly confined to one organ. With regard to the isolated lesions of the appendix, there is some suggestion that the arteritis, discovered incidental to routine histologic examination, may not merit the ominous prognosis of periarteritis nodosa, despite the microscopic resemblance. On the other hand, fatal periarteritis nodosa certainly may involve an appendix removed surgically (Spiegel), so that a blanket dismissal of these lesions is unwarranted at present.

## DIABETIC GLOMERULOSCLEROSIS

### Introduction

Up until 1936, the only renal lesion more or less specifically associated with diabetes mellitus was the glycogenic vacuolization of the tubular epithelium of the loops of Henle. In that year, attention was directed to an important contribution by Kimmelstiel and Wilson. They described a form of glomerulosclerosis that tended to occur in diabetic patients with hypertension, retinopathy, albuminuria, hypoproteinemia and edema. For a while this clinicopathologic association was treated with difficulty for several reasons. First, those authors stated that the lesions were found "fre-

quently," an observation not subsequently borne out, but one which, at the time, probably discouraged interest somewhat. Second, they were of the erroneous impression that these peculiar globular lesions were merely histologically well advanced stages of the glomerular changes which they termed senile (arterial) nephrosclerosis. Their identification of the diabetic glomerulosclerosis with simple senile nephrosclerosis diminished interest even further. Finally, it seemed unlikely to most casual observers that the significance of a distinctive glomerular lesion could have been badly missed for so many decades by the most astute renal investigators.

Within five years, however, several reports appeared which, when pieced together, indicated that the clinical findings might indeed represent a genuine syndrome with a histologic counterpart, but there were two dissenting reports which are still difficult to explain. In one of these (Horn and Smetana) it was stated that diabetic glomerulosclerosis occurred actually more commonly in nondiabetics than in diabetics, the other (Christian) concluded that the lesion was entirely nonspecific.

In 1941 (Allen), the histologic lesion was defined in detail. It was shown to be common in diabetic patients over the age of 40, to be practically specific for diabetes, to be a distinctive form of glomerular *capillary* sclerosis rather than an *intercapillary* sclerosis, and to be far and away the most reliable histologic criterion for the diagnosis of diabetes mellitus at postmortem. Thereafter, a plethora of reports appeared over the next decade which appear to have confirmed the conclusions reached a decade ago. Most of the details which follow are from the report published at that time and are still valid.

### Frequency of the Lesion

The lesion occurs in approximately *one out of three diabetic patients over the age of 40* (Allen). Elsewhere, the reported incidence ranges from 20 per cent (Robbins) to 63.7 per cent (Laipple) for diabetic patients of all ages. Undoubtedly, the figure of 63.7 per cent can be explained by the inclusion of cases that do not meet all the histologic criteria. That this is so

PLATE 235. PERIARTERITIS NODOSA



FIG A *Ischemic alteration of the epithelium of the more vulnerable proximal tubules in periarteritis nodosa. The cells of the altered proximal tubules come to resemble those of the distal tubules. This histologic picture simulates the so-called "endocrine kidney" (of Selye) produced experimentally by partial occlusion of a renal artery with or without ureteral occlusion.*

FIG B *Cortical depression following ischemic atrophy due to periarteritis nodosa. The involved vessel and thrombus is at the right of the photograph.*

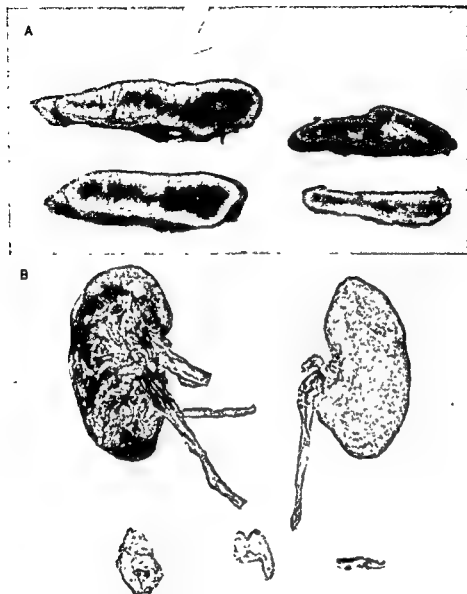


FIG. A. Diffuse hyperplasia of adrenal glands in association with periarthritis nodosa, hypertension and Cushing's syndrome. The hyperplastic glands are at the left, normal adrenals are shown at the right for the contrast.

FIG. B. Periarthritis nodosa associated with hyperplasia of adrenal glands. Thrombosed vessels of periarthritis nodosa are visible in the adrenal glands at the bottom of the photograph.

is indicated not only by two of their four photomicrographs but by their disputed finding of the lesion in 12.5 per cent of subacute and chronic glomerulonephritis.

### *Age and Sex Incidence*

In most series (Bell, Henderson et al ; Rifkin et al ; Siegel and Allen), there is a preponderance of females. The lesion occurs infrequently below the age of 40. Only one (aged 34) was found in our series (Siegel and Allen) and none in Bell's material below the age of 30, the youngest reported case to date is 16 years of age (Laippley et al.). We have reviewed many instances of chronic lobular glomerulonephritis (plate 245E) in young patients whose renal lesions have been mistaken for those of diabetic glomerulosclerosis.

### *Specificity of the Lesion of Diabetic Glomerulosclerosis*

Much unfortunate confusion has resulted from the publication of data indicating the occurrence of the lesion of diabetic glomerulosclerosis in a remarkably large number of nondiabetic patients (Horn and Smetana, Henderson et al., Laippley et al.; Goodof). In one series (Goodof) the lesions were found in 30 per cent of nondiabetic patients over the age of 70. In contrast, we have found the lesion only once in a nondiabetic (on whom no glucose tolerance curve had been done). Bell also has seen the nodular lesion of diabetic glomerulosclerosis in only one nondiabetic. At four large institutions [Memorial Hospital, New York, the Kingsbridge Veterans Hospital, the Army Institute of Pathology (1942-1946) and the Mallory Institute of Pathology (Robbins)], the lesion of diabetic glomerulosclerosis has not been found in a single nondiabetic patient. Therefore, it appears reasonable to conclude that reports of nonspecificity are based principally on the inclusion of extraneous lesions in the group. Another possible source of misinterpretation is the fact that diabetes in these elderly patients is usually mild, often requiring no insulin for control, and the renal threshold for glycosuria may be elevated (Minsky and Nelson). Hence, the elimination of the diagnosis of diabetes mellitus merely on the absence of

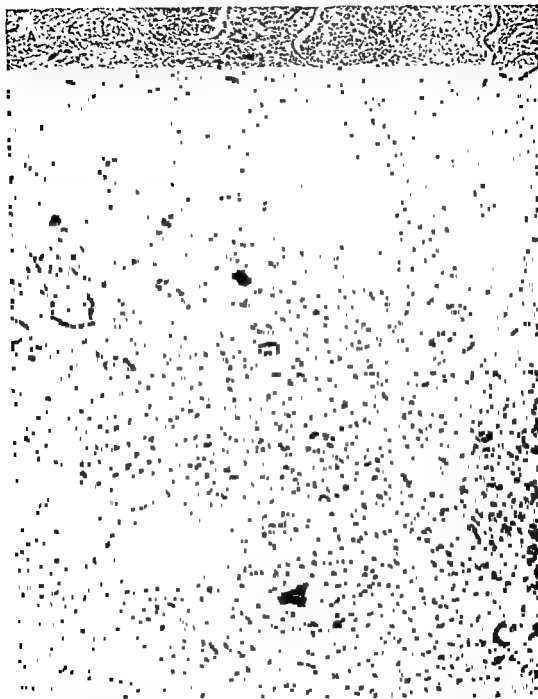
glycosuria unjustifiably masks a number of cases.

In conclusion, then, the characteristic nodular lesion of diabetic glomerulosclerosis may be considered specific for all practical purposes. This conclusion is further supported by the experimental production of the lesion in diabetic animals (Lukens and Dohan).

### *Clinical Picture*

Diabetic glomerulosclerosis may occur without any symptoms related thereto. In such cases, it may be assumed that the lesions are sparse, involving only a few scattered glomeruli. If the lesions are numerous and are present in practically all of the glomeruli (grade 4+ on a scale 1+ to 4+), it may then be assumed, with great odds, that the entire clinical complex of diabetes, hypertension and the nephrotic syndrome is present. Conversely, if the patient presents himself with the full clinical picture, the likelihood of diabetic glomerulosclerosis being found is also great. However, because other renal lesions, such as amyloidosis and some forms of chronic glomerulonephritis, may also result in the nephrotic syndrome in a diabetic patient, these two possibilities must be taken into diagnostic account. Intermediate grades of severity of the clinical syndrome are generally associated with more or less corresponding degrees of diabetic glomerulosclerosis (Siegel and Allen).

As stated, the diabetes is usually mild, often requiring little or no insulin for control. The diabetes apparently precedes the development of the lesions from 3 to 20 years or more (Siegel and Allen). We have seen one diabetic patient in whom the lesions were present in the one kidney at autopsy but were absent in the kidney removed surgically three years previously. This case parallels that of Derow, Altschule, and Schlesinger in which the lesions appeared to take four years to develop. Hypertension and hypertensive retinopathy are almost constant when diabetic glomerulosclerosis is widespread. Azotemia, at times associated with myocardial failure occurs in about 75 per cent of cases of severe diabetic glomerulosclerosis and frequently progresses to uremia. Hypoproteinemia with reversal of the albumin-globulin ratio,



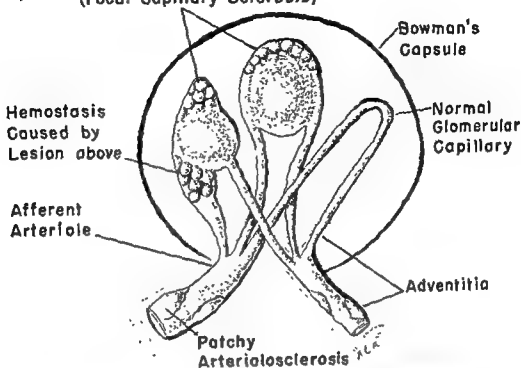
FIGS. A AND B. *Granulomatous giant cell arteritis of arcuate and interlobar arteries, considered to represent an allergic reaction akin to periarteritis nodosa. Similar reactions have been attributed to sulfonamides, none was used in this case.*



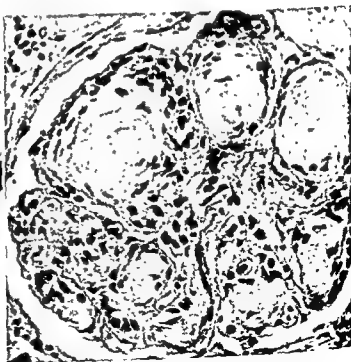
PLATE 238. DIABETIC GLOMERULOSCLEROSIS

**Diabetic Glomerulosclerosis  
(Focal Capillary Sclerosis)**

**A**



**B**



**FIG A** The origin from the capillary wall of the lesion of diabetic glomerulosclerosis is diagrammatically illustrated. The capillary bulge causes a stenosis of the capillary lumen as well as marked dilatation.

**FIG B** The kidney with diabetic glomerulosclerosis usually is of normal or greater than normal size and has the stigmata of arterial and arteriolar nephrosclerosis.

**FIG C** Thin, unusually dilated capillaries and lamination of endothelial cells and fibers are characteristic of the periphery of the hyaline masses of diabetic glomerulosclerosis.

and hypercholesterolemia is common and appears to be related to the albuminuria. Of course a fraction of the hypercholesterolemia may be an intrinsic part of the diabetes mellitus and independent of the nephrotic syndrome.

### *Prognosis*

With the development of the complete renal component of the syndrome, the prognosis becomes grave and life expectancy is about two to three years. Death is likely to result from uremia and/or cardiac failure.

### *Pathology*

#### *Gross appearance*

Not only are the kidneys with diabetic glomerulosclerosis not contracted, but they are likely to be slightly to moderately larger than normal (plate 238B). Such enlargement is characteristic of kidneys from patients with the clinical nephrotic syndrome (albuminuria, hypoproteinemia, reversal of albumin-globulin ratio, edema and hypercholesterolemia) from other causes such as amyloidosis, and chronic membranous or lobular glomerulonephritis.

#### *Histologic appearance (plates 238 to 247)*

The lesions in the kidneys may be diffuse or sparse. They may involve practically all of the glomeruli in a section or merely one, and this isolated lesion may be quite as typical as those in the more extensively affected kidneys. They characteristically show much variability in size, ranging from approximately 20 microns to about 120 microns in their greatest diameter. Hence, a large lesion may occupy more than a third of the volume of a glomerulus. The lesions are generally more or less spherical although occasional oval ones are seen, with the longer diameter two or three times the other. There is a tendency for the initial lesion or the largest lesion to be opposite, rather than adjacent, to the vascular pole of the glomerulus (plate 241B). The involved glomeruli, in spite of the hyalinization, need not be small; they may be as large or frequently larger than normal. In small glomeruli the hyaline mass may bulge the portion of Bowman's capsule immediately about it. Bowman's space may be of normal width, not infrequently, however, it is widened

and may be filled with protein and lipid precipitate.

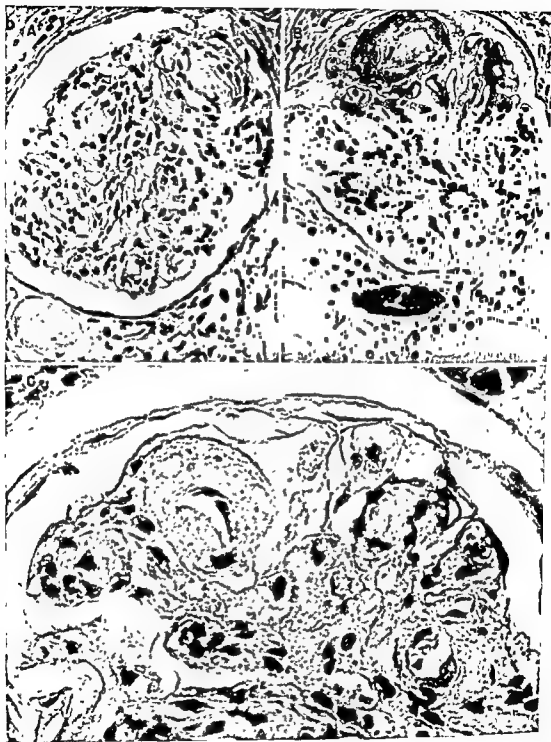
The typical lesion consists of hyalinized acidophilic material, which with low magnification appears almost completely homogeneous. With greater magnification, there is a circumferentially laminated structure, often pitted with a few small vacuoles (plate 239C). The fibrillated hyalin is dull and dense appearing, manifesting little or none of the refractility of the "wire-loops" seen in the glomeruli of acute disseminated lupus erythematosus. The acidophilia of the lesions, as a rule, is not quite as marked as that of the walls of the appertaining arterioles. The hyalin does not react positively with stains for amyloid or fat.

The cellularity of the lesions varies in quantity, disposition and character. Often there are two or three peripheral concentric layers of flattened cells (plate 241A). These appear to be mostly displaced endothelial and occasional epithelial cells. The core is generally devoid of cells, although occasional vesicular or more or less pyknotic distorted nuclei, and even a red blood cell or two, may be found near the center (plate 241A). The impression that in some of the lesions there is an increase of cells results from a tangential section passing through the cellular rim at the periphery of the lesion (plate 241D). A few endothelial and epithelial foam cells are seen (plate 239C).

#### *Capillary vs. intercapillary origin*

Reconstruction of the lesion from serial sections reveals that it is not an *intercapillary* mass or bar of hyalin which extends from the hilar arterioles to the periphery of the glomerulus, as Kimmelstiel and Wilson have believed. Rather, it is a mass of hyalin formed by an abrupt thickening of the wall of one or more closely situated capillaries, with resultant encroachment on and often obliteration of their lumens (Allen). These lumens are almost invariably obliterated in sections through the "equator" of the mass or through its great arcs, but near the poles of the globes, that is, as one approaches tangential sections, lumens containing red blood cells and lined by endothelium become apparent (plate 239C). In kidneys with widespread lesions, there may be observed in a

PLATE 239. DIABETIC GLOMERULOSCLEROSIS



FIGS A AND B *Diabetic glomerulosclerosis* showing bland afferent arteriosclerosis and evolutionary stages of glomerulosclerosis, indicating the origin of the lesions from sclerosis of capillary walls rather than from "intercapillary" tissue. Note that the capillary lumens are still unobliterated by the sclerotic walls of the incomplete lesion.

FIG C *Diabetic glomerulosclerosis* clearly originating from sclerosis of capillary walls rather than from so-called intercapillary mesangium. Endothelial cells are vacuolated by lipid.



FIG. A The lesion of diabetic glomerulosclerosis is essentially free of fat, as here shown. The hyaline (black) is in endothelial and epithelial cells, in Bowman's capsule and focally in the afferent arterioles (Sud in III stain). Anisotropic fat occurs in the proximal convoluted tubules not only with diabetic glomerulosclerosis but with amyloidosis (figure C) and other conditions associated with the nephrotic syndrome.

FIG. B Diabetic glomerulosclerosis showing that the hyalinized glomerular lesion is free of fat (black) which is present in Bowman's space and capsule (Sud in III stain).

FIG. C Amyloidosis of glomerulus which simulates diabetic glomerulosclerosis. There is also lipid vacuolization of the proximal convoluted tubules. This combined picture indicates that the patient had the clinical nephrotic syndrome.

single section of a glomerulus the crude equivalent of serial sections, in the form of a variety of transitional phases of the multiple lesions in different parts of the tuft (plate 239A). In such glomeruli there may be normal capillary loops, loops of which only a crescentic segment has undergone the characteristic hyalinization, loops of which the entire wall has become hyalinized so as to leave only a narrow lumen containing one or two red blood cells, and, finally, the typical hyaline disc in which the lumen has been obliterated.

### *Glomerular permeability*

A characteristic and, physiologically, probably important component of the lesion is dilatation of the capillaries situated at the rim of the lesion. Immediately external to the hyaline mass, the capillary walls are thinned, lobulated and practically constantly dilated at some level of their course as observed in serial sections. Commonly there is a single capillary loop partially or completely circumscribed about a large diabetic lesion. Even though the space between the centrally placed disc and the external wall of such capillaries may appear deceptively small, it is obvious that these capillaries, encircling, as they do, the large hyaline mass, are greatly dilated (plate 242A). These peripheral capillaries may be jammed solid with red blood cells, or they may contain laked blood and much protein precipitate, some of which may have escaped into Bowman's space. The most strikingly dilated loops may contain small clots composed of a delicate fibrin mesh and platelets. The walls of these distended capillaries have escaped thickening and have been stretched excessively, as if the diabetic lesion had caused a stenosis of the capillary lumen with consequent proximal dilatation (plate 238A). The possible physiologic significance of this finding will be discussed.

Of course, in the same section, there are, in addition, glomeruli which exhibit the changes characteristic of ordinary nephrosclerosis. These changes may be present in the very same glomeruli involved by the diabetic lesion and may be easily distinguishable from the latter. The simple nephrosclerotic portions of the glomeruli are differentiated by several criteria,

chief among which is the feature that no one capillary loop appreciably outstrips its neighbor in degree of hyalinization. This holds even in the most advanced cases of nephrosclerosis and is in contrast to the typically focal hyalinization in the diabetic kidney (plate 245).

*Special stains*—With the Mallory-Heidenhain stain, the diabetic lesions are the deep blue of collagen, as a rule, but incompletely collagenized foci stain pink or purple orange. Although the crescentic foci of thickening of capillary walls of the early lesions are easily noted in routine sections, they are perhaps more clearly visualized with the special stains for collagen. The red blood cells within the lumen of an evolving lesion leave no doubt of its capillary rather than intercapillary genesis (plate 241A, 242B, 243C, 244D, 245E, 246F, 247G, 248H, 249I, 250J, 251K, 252L, 253M, 254N, 255O, 256P, 257Q, 258R, 259S, 260T, 261U, 262V, 263W, 264X, 265Y, 266Z, 267A, 268B, 269C, 270D, 271E, 272F, 273G, 274H, 275I, 276J, 277K, 278L, 279M, 280N, 281O, 282P, 283Q, 284R, 285S, 286T, 287U, 288V, 289W, 290X, 291Y, 292Z, 293A, 294B, 295C, 296D, 297E, 298F, 299G, 300H, 301I, 302J, 303K, 304L, 305M, 306N, 307O, 308P, 309Q, 310R, 311S, 312T, 313U, 314V, 315W, 316X, 317Y, 318Z, 319A, 320B, 321C, 322D, 323E, 324F, 325G, 326H, 327I, 328J, 329K, 330L, 331M, 332N, 333O, 334P, 335Q, 336R, 337S, 338T, 339U, 340V, 341W, 342X, 343Y, 344Z, 345A, 346B, 347C, 348D, 349E, 350F, 351G, 352H, 353I, 354J, 355K, 356L, 357M, 358N, 359O, 360P, 361Q, 362R, 363S, 364T, 365U, 366V, 367W, 368X, 369Y, 370Z, 371A, 372B, 373C, 374D, 375E, 376F, 377G, 378H, 379I, 380J, 381K, 382L, 383M, 384N, 385O, 386P, 387Q, 388R, 389S, 390T, 391U, 392V, 393W, 394X, 395Y, 396Z, 397A, 398B, 399C, 400D, 401E, 402F, 403G, 404H, 405I, 406J, 407K, 408L, 409M, 410N, 411O, 412P, 413Q, 414R, 415S, 416T, 417U, 418V, 419W, 420X, 421Y, 422Z, 423A, 424B, 425C, 426D, 427E, 428F, 429G, 430H, 431I, 432J, 433K, 434L, 435M, 436N, 437O, 438P, 439Q, 440R, 441S, 442T, 443U, 444V, 445W, 446X, 447Y, 448Z, 449A, 450B, 451C, 452D, 453E, 454F, 455G, 456H, 457I, 458J, 459K, 460L, 461M, 462N, 463O, 464P, 465Q, 466R, 467S, 468T, 469U, 470V, 471W, 472X, 473Y, 474Z, 475A, 476B, 477C, 478D, 479E, 480F, 481G, 482H, 483I, 484J, 485K, 486L, 487M, 488N, 489O, 490P, 491Q, 492R, 493S, 494T, 495U, 496V, 497W, 498X, 499Y, 500Z, 501A, 502B, 503C, 504D, 505E, 506F, 507G, 508H, 509I, 510J, 511K, 512L, 513M, 514N, 515O, 516P, 517Q, 518R, 519S, 520T, 521U, 522V, 523W, 524X, 525Y, 526Z, 527A, 528B, 529C, 530D, 531E, 532F, 533G, 534H, 535I, 536J, 537K, 538L, 539M, 540N, 541O, 542P, 543Q, 544R, 545S, 546T, 547U, 548V, 549W, 550X, 551Y, 552Z, 553A, 554B, 555C, 556D, 557E, 558F, 559G, 560H, 561I, 562J, 563K, 564L, 565M, 566N, 567O, 568P, 569Q, 570R, 571S, 572T, 573U, 574V, 575W, 576X, 577Y, 578Z, 579A, 580B, 581C, 582D, 583E, 584F, 585G, 586H, 587I, 588J, 589K, 590L, 591M, 592N, 593O, 594P, 595Q, 596R, 597S, 598T, 599U, 600V, 601W, 602X, 603Y, 604Z, 605A, 606B, 607C, 608D, 609E, 610F, 611G, 612H, 613I, 614J, 615K, 616L, 617M, 618N, 619O, 620P, 621Q, 622R, 623S, 624T, 625U, 626V, 627W, 628X, 629Y, 630Z, 631A, 632B, 633C, 634D, 635E, 636F, 637G, 638H, 639I, 640J, 641K, 642L, 643M, 644N, 645O, 646P, 647Q, 648R, 649S, 650T, 651U, 652V, 653W, 654X, 655Y, 656Z, 657A, 658B, 659C, 660D, 661E, 662F, 663G, 664H, 665I, 666J, 667K, 668L, 669M, 670N, 671O, 672P, 673Q, 674R, 675S, 676T, 677U, 678V, 679W, 680X, 681Y, 682Z, 683A, 684B, 685C, 686D, 687E, 688F, 689G, 690H, 691I, 692J, 693K, 694L, 695M, 696N, 697O, 698P, 699Q, 700R, 701S, 702T, 703U, 704V, 705W, 706X, 707Y, 708Z, 709A, 710B, 711C, 712D, 713E, 714F, 715G, 716H, 717I, 718J, 719K, 720L, 721M, 722N, 723O, 724P, 725Q, 726R, 727S, 728T, 729U, 730V, 731W, 732X, 733Y, 734Z, 735A, 736B, 737C, 738D, 739E, 740F, 741G, 742H, 743I, 744J, 745K, 746L, 747M, 748N, 749O, 750P, 751Q, 752R, 753S, 754T, 755U, 756V, 757W, 758X, 759Y, 760Z, 761A, 762B, 763C, 764D, 765E, 766F, 767G, 768H, 769I, 770J, 771K, 772L, 773M, 774N, 775O, 776P, 777Q, 778R, 779S, 780T, 781U, 782V, 783W, 784X, 785Y, 786Z, 787A, 788B, 789C, 790D, 791E, 792F, 793G, 794H, 795I, 796J, 797K, 798L, 799M, 800N, 801O, 802P, 803Q, 804R, 805S, 806T, 807U, 808V, 809W, 810X, 811Y, 812Z, 813A, 814B, 815C, 816D, 817E, 818F, 819G, 820H, 821I, 822J, 823K, 824L, 825M, 826N, 827O, 828P, 829Q, 830R, 831S, 832T, 833U, 834V, 835W, 836X, 837Y, 838Z, 839A, 840B, 841C, 842D, 843E, 844F, 845G, 846H, 847I, 848J, 849K, 850L, 851M, 852N, 853O, 854P, 855Q, 856R, 857S, 858T, 859U, 860V, 861W, 862X, 863Y, 864Z, 865A, 866B, 867C, 868D, 869E, 870F, 871G, 872H, 873I, 874J, 875K, 876L, 877M, 878N, 879O, 880P, 881Q, 882R, 883S, 884T, 885U, 886V, 887W, 888X, 889Y, 890Z, 891A, 892B, 893C, 894D, 895E, 896F, 897G, 898H, 899I, 900J, 901K, 902L, 903M, 904N, 905O, 906P, 907Q, 908R, 909S, 910T, 911U, 912V, 913W, 914X, 915Y, 916Z, 917A, 918B, 919C, 920D, 921E, 922F, 923G, 924H, 925I, 926J, 927K, 928L, 929M, 930N, 931O, 932P, 933Q, 934R, 935S, 936T, 937U, 938V, 939W, 940X, 941Y, 942Z, 943A, 944B, 945C, 946D, 947E, 948F, 949G, 950H, 951I, 952J, 953K, 954L, 955M, 956N, 957O, 958P, 959Q, 960R, 961S, 962T, 963U, 964V, 965W, 966X, 967Y, 968Z, 969A, 970B, 971C, 972D, 973E, 974F, 975G, 976H, 977I, 978J, 979K, 980L, 981M, 982N, 983O, 984P, 985Q, 986R, 987S, 988T, 989U, 990V, 991W, 992X, 993Y, 994Z, 995A, 996B, 997C, 998D, 999E, 1000F).

those of the azocarmine stain.

The silver stain (Foot's modification of the Bielschowsky stain) is of particular help in the analysis of the lesion. Characteristically, the diabetic hyaline body which stains a more or less homogeneous pink with hematoxylin-eosin, is found to be composed of a mass of black or deep brown fibers, which are often laminated and are easily and sharply differentiated from the uninvolved portions of the glomerulus. Even the crescentic mural capillary thickenings of the early or small lesions are revealed as laminations of argyrophilic or dense collagenous fibers (plate 243). The remarkable feature is the pronounced difference between the argyrophilia of the diabetic lesions and the relatively slight affinity, with the Bielschowsky stain, of the remaining capillary loops even within the same glomerulus, however atrophied this structure may be. Some of the large lesions show argyrophilic fibers at the periphery while the core stains the golden or deep brown characteristic of collagen. This brown coloration differs distinctly from the pink of the counter-stained, atrophied capillaries of the nonspecific sclerotic portions of the glomerulus. The hyalin of the diabetic lesion thus becomes distinguishable with a high degree of reliability from the hyalin of the simple nephrosclerotic lesion in the glomerulus. It might be added that, in tinctorial

PLATE 241. DIABETIC GLOMERULOSCLEROSIS

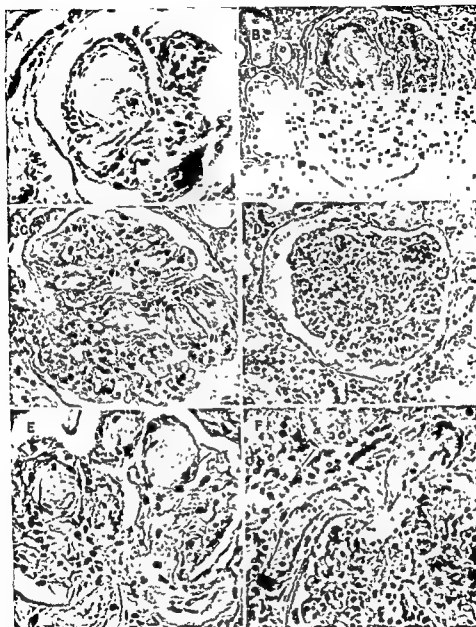


FIG. A Capillary origin of diabetic glomerulosclerosis. Red blood cells are present in the lumen of the incompletely formed lesion. Hematuria is absent or mild.

FIG. C Diabetic glomerulosclerosis showing the origin from capillary walls. The remainder of the tuft shows the picture of so-called diffuse glomerulosclerosis, of questionable diagnostic value by itself.

FIG. B The early lesion of diabetic glomerulosclerosis is located characteristically opposite the vascular pole. The laminated cells are seen at the periphery of the sphere.

FIG. D A cellular focus as in the above photograph results from a tangential section through the cellular periphery of a lesion.

FIGS. E AND F Efferent as well as afferent arteriosclerosis in diabetic glomerulosclerosis. Efferent arteriosclerosis is common in advanced diabetic glomerulosclerosis and rare, or absent, in other diseases of the kidney.

properties, the hyalin of the diabetic lesions differs too from that found in the ovarian, uterine and splenic vessels and from the hyalin present in the islets of Langerhans (plate 243D). The unmistakable contrast between the scanty argyrophilia of the pancreatic islets and the abundant argyrophilia of the glomerular lesions in diabetes clearly and significantly differentiates the two types of hyalin. Moreover, the hyalin of the islets also stains (if inconstantly) with metachromatic stains for amyloid.

#### *Fat stains*

There is commonly a moderate amount of fat, chiefly neutral but some anisotropic, located principally in the proximal convoluted tubules and in arterioles and interlobular arteries. Crescentic deposits of sudanophilic material are also found in Bowman's space (plate 240A). A few fat droplets are dispersed in endothelial and epithelial cells within glomeruli. The diabetic lesion itself usually contains no fat or just scattered minute droplets. The diagnostic value of birefringent lipiduria has recently been emphasized (Rifkin et al.). However, birefringent lipids may be found in the urine in all varieties of disease with the clinical nephrotic syndrome including diabetic glomerulosclerosis, amyloidosis and chronic nephrotic glomerulonephritis. Nevertheless, the finding of anisotropic fat may be of help in distinguishing renal from extra-renal edema.

#### *Glycogen*

The Armanni-Ebstein or glycogen vacuoles in the loops of Henle are rarely found. This is hardly surprising inasmuch as these vacuoles

are commonly associated with severe, uncontrolled cases of diabetes mellitus.

#### *Tryptic digestion*

In an attempt to define further the particular type of hyalin in these kidneys and to distinguish the hyalin of the diabetic glomerular lesions from that of the arterioles, the digestibility with trypsin was determined. The following are the observations made after digestion by trypsin for an average of 24 hours at 37°C. The solution was alkalinized with sodium carbonate and 1 cc. of chloroform was added for its preservative action (Allen).

1. The diabetic lesion, as a rule, manifested marked resistance to trypsin. This is in keeping with the frequent argyrophilia and dense collagenous composition of the lesions.

2. The remainder of the capillary loops, that is, those in the nonspecific sclerotic portions of the glomeruli, exhibit slight digestibility. This is demonstrated by the diminished affinity for aniline blue of these loops in sections exposed to trypsin, as contrasted with the undigested control slide with the diabetic lesions in the same section or even the very same glomerulus (plate 242C).

3. The thickened Bowman's capsule and the basement membrane of the tubules resist digestion. These are argyrophilic.

4. A contrast is offered by the digestibility of the hyalinized portions of the arterioles. This pertains principally to the central parts of the arteriolar walls, since the inner and outermost portions are often argyrophilic and hence indigestible.

*Hyalin involvement of the arterioles.* There appears to be a practically constant association

FIG. A. Cavernous dilatation of capillaries at the periphery of a lesion of diabetic glomerulosclerosis. This is a common phenomenon in various degrees about most lesions of diabetic glomerulosclerosis, but may require serial sections to detect (Goldner's modification of Masson's trichrome stain).

FIG. D. Capillary sclerosis as the morphologic basis of the lesion of diabetic glomerulosclerosis is detected in several of these incompletely developed lesions. Red blood cells are actually in the lumens of the capillaries, the walls of which are focally thickened (arrow).

FIG. B. Peripheral dilatation of thin walled capillary (arrows), many sites of mural origin of diabetic glomerulosclerosis are also shown.

FIG. C. Resistance to tryptic digestion of lesion of diabetic glomerulosclerosis is demonstrated by obvious contrast with the remainder of the tuft (Tryptic digestion and Mallory-Heidenhain stain).

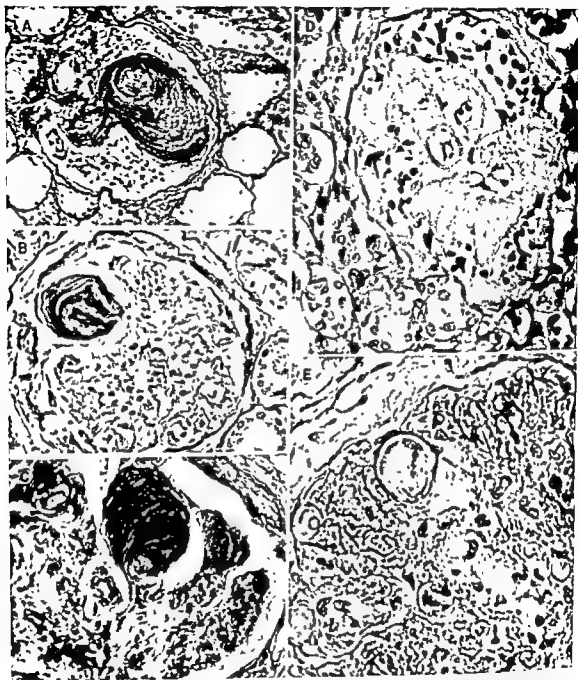
FIG. E. Capillary origin of diabetic glomerulosclerosis, formation of earliest lesions opposite the vascular pole and focal capillary sclerosis are demonstrated in this photograph.

PLATE 242. DIABETIC GLOMERULOSCLEROSIS



(Legends on facing page)





FIGS A, B, AND C *Laminated argyrophilia* is characteristic of the lesions of diabetic glomerulosclerosis. There is a striking and fundamentally significant contrast in affinity for silver between the diabetic lesion and the remainder of the tuft made sclerotic by aging or benign nephrosclerosis (Biel-schowsky's silver stain)

FIG D *Hyalin in the islets of Langerhans* of the pancreas is different in composition from that of diabetic glomerulosclerosis. The argyrophilia of the islets is sparse and scattered (Modified Biel-schowsky's silver stain)

of diabetic glomerulosclerosis (Modified Biel-schowsky's silver stain)



of the diabetic lesion with afferent arteriolo-sclerosis. Only rarely are lesions found in glomeruli whose afferent arterioles are thin walled. Occasionally the arterioles may appear normal in a single section, however, because of the uneven, in places, discontinuous thickening that may be present in these vessels (plate 240A), there may be found a markedly thickened segment elsewhere along their course if the sections are examined serially.

A finding of considerable interest is the thickening and narrowing of the *efferent arterioles* by a hyaline material identical with that in the afferent arterioles. The efferent vessels are, as a rule, not as strikingly thickened as the afferent ones, nor are they as constantly affected. For example, in one of the more severely involved kidneys, only about a third of the efferent arterioles were thickened and narrowed as opposed to a practically constant involvement of the afferent arterioles.

The hyalin of the arterioles differs in several respects from that of the diabetic glomerular lesions. First, there is usually a much greater abundance of fat in the arteriolar walls (plate 240A). As a matter of fact, the fully collagenized diabetic lesions may contain no fat. Second, the arteriolar hyalin is generally more intensely eosinophilic. In addition, there is frequently present a basophilic tint in the hyalin of the arterioles stained with hematoxylin-eosin, which is found in the midportions of the wall so as to correspond to a highlight. This tint signifies a "soft" hyalin that is digestible with trypsin and does not take the stains for collagen. Third, the arteriolar hyalin is typically bright red with the azocarmine stain, whereas the diabetic lesions are predominantly blue, indicating the collagenization of the latter. Fourth, they lack the resistance to tryptic digestion so characteristic of the diabetic lesions (plate 242C). Finally, there is a distinct difference in the amount and distribution of the argyrophilic fibers in the two locations (plate 243). Similar though less marked changes may be seen in the afferent arterioles of nephrosclerotic kidneys from nondiabetic patients, with the absence, however, of the diabetic glomerular lesions. The prearteriolar interlobular arteries are also frequently thickened and

narrowed by irregular hillocks of azocarmophilic hyalinized material.

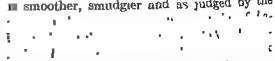
#### *Vascular sclerosis vs lack of renal contraction*

There may be a remarkable disparity between the degree of vascular involvement, on the one hand, and the relative lack of gross renal contraction and granularity, on the other. This feature was noted by Kimmelstiel and Wilson, who felt that the "contraction may be in part or completely obscured by the signs of nephrosis." What this means in terms of actual histologic changes is not clear. Surprisingly enough, it is not a simple matter to account for the illusory smoothness and enlargement of the kidneys even from the sections themselves. To be sure, there usually are numerous areas of cortical atrophy (although this need not be marked even with extensive diabetic glomerular lesions) alternating with foci of dilated tubules, yet without the expected proportionate gross granularity and contraction. Failing a micrometric examination, the only morphologic clue one gets is that the scar tissue is edematous and not as compact as in benign nephrosclerosis and that the tubular epithelium is focally swollen with fat.

#### *Differential Histologic Diagnosis*

The lesions of diabetic glomerulosclerosis have been confused with (1) amyloidosis, (2) nonspecific glomerulosclerosis of any atrophic kidney, (3) chronic lobular (nephrotic) glomerulonephritis, (4) focal endocarditic glomerulonephritis and (5) "wire-loop" glomerulitis of disseminated lupus erythematosus.

#### *Amyloidosis*

In routine sections stained with hematoxylin and eosin, the hyalin of the glomerular amyloid is smoother, smudgier and as judged by the  
  
 marks, and the peripheral rows of nuclei of the diabetic lesion, are generally lacking in amyloidosis. In addition, the amyloidosis, in contrast to the diabetic lesion, may also conspicuously involve the tubular basement membranes and arteries in a distinctive manner (plate 251B).

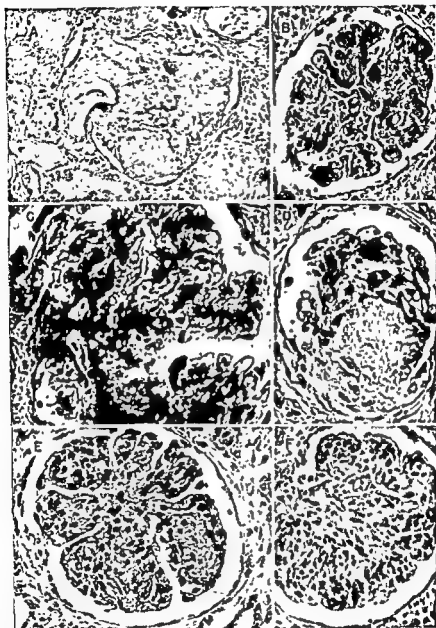


FIG A Glomerular amyloidosis. The efferent arteriole is occasionally involved in amyloidosis

FIG C Hypertensive glomerulus of benign nephrosclerosis with capillary sclerosis (Elastica-van Gieson stain)

FIG E Chronic lobular glomerulonephritis with characteristically uniform lobulation which involves all the glomeruli

FIG B Disseminated lupus erythematosus with verrucal capillaritis due to exaggerated fibrinoid swelling

FIG D Chronic sclerosing glomerulonephritis with focal sclerosis of the tuft

FIG F Chronic nephrotic glomerulonephritis partially lobular and partially membranous

PLATE 246. DIABETIC GLOMERULOSCLEROSIS: DIFFERENTIAL HISTOLOGIC DIAGNOSIS

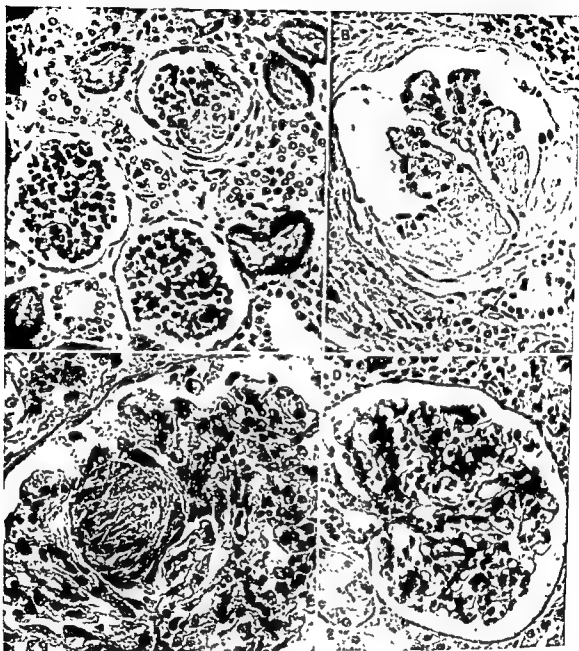


FIG. A Congenital glomerulosclerosis, an incidental finding in the kidney of an infant

FIG. C Focal endocarditic glomerulonephritis ("focal embolic glomerulonephritis") simulating the lesion of diabetic glomerulosclerosis

FIG. B Sclerotic atrophy of glomerulus in hydro-nephrosis

FIG. D Unusual variant of focal endocarditic glomerulonephritis in a nondiabetic with subacute bacterial endocarditis, simulating the so-called diffuse diabetic glomerulosclerosis

The peripheral dilatation of capillaries about the amyloidotic spheres is similar to that about the lesions of diabetic glomerulosclerosis. In our material, the Foot modification of the Bielschowsky stain reveals little argyrophilia in glomerular amyloidosis in contrast to the argyrophilia of diabetic glomerulosclerosis and in contrast to the result published by King. Even in the latter case, the argyrophilia of amyloidosis lacked the constant laminations of the silver fibers of diabetic glomerulosclerosis.

#### *Non-specific glomerulosclerosis of atrophic kidneys*

Sclerotic glomeruli of atrophic glomerulonephritis, pyelonephritic, nephrosclerotic (benign) and infarcted kidneys have been mistaken for the sclerosis of diabetic glomerulosclerosis (plate 245, 246). If the clean sharpness of outline of the nodular diabetic lesion, along with the peripheral capillary ring and nuclei, as well as the contrast with the thin-walled capillaries of the other parts of the tuft, is kept in mind, this type of error in diagnosis may be avoided.

#### *Chronic lobular glomerulonephritis*

Second to the lesions of glomerular amyloidosis, chronic lobular glomerulonephritis is most easily confused with diabetic glomerulosclerosis. The problem is made especially difficult because both lesions may be accompanied by the nephrotic syndrome. The lesions of lobular glomerulonephritis tend to be of uniform size and to involve every glomerulus in both kidneys (plate 80, 245E). In addition, the peripheral capillaries about the hyaline sphere are likely to be reduplicated and slightly frayed in contrast to the delicate wall of the peripheral capillaries about the diabetic hyaline spheres. The differentiation, therefore, may be made with routine stains. As an additional differential fact, however, it should be mentioned that with the silver stain the spherical lesions of chronic lobular glomerulonephritis are found to be made up of a mass of short curly coils of silver fibrils in contrast to the laminations of diabetic glomerulosclerosis (plate 243).

#### *Focal endocarditic glomerulonephritis*

Occasionally the collagenized lesion of focal endocarditic glomerulonephritis simulates dia-

betic glomerulosclerosis. Here, too, the endocarditic lesions lack the sharp outlines and peripheral capillaries of the diabetic spheres and, moreover, are prone to be irregularly fused with Bowman's capsule or adjacent capillaries. The silver stain also reveals them to be made up of irregular fibrils (plate 244).

#### *"Wire-loop" glomerulonephritis of disseminated lupus erythematosus*

In routine hematoxylin-eosin stains there need be no problem of differentiating the "wire-loop" lesions from those of diabetic glomerulosclerosis. The glomerular change of lupus erythematosus is an alteration of a portion of capillary wall that may swell into the capillary lumen as a verrucal hillock (plate 245B). However, the capillary change in this disease is a soft fibrinoid, brightly acidophilic swelling without an envelope of thin-walled capillaries. This fibrinoid alteration is not of the order of the dull hard dense hyalin of the diabetic glomerulosclerosis.

#### *Summary of Diabetic Glomerulosclerosis*

1 Diabetic glomerulosclerosis is a lesion specific for diabetes mellitus if the rarest equivocal cases are excepted.

2 Diabetic glomerulosclerosis occurs in one of three diabetic patients over the age of 40 and is extremely uncommon below the age of 30.

3 Patients with a few isolated lesions of diabetic glomerulosclerosis manifest no renal symptoms on this basis, those with widespread diabetic glomerulosclerosis very likely will have, in addition to the diabetes mellitus, hypertension, diabetic retinopathy, albuminuria, edema, hypoproteinemia, hypercholesterolemia and renal insufficiency. Prognosis is grave after the development of these signs and symptoms.

4 Sclerosis of the usually histologically neglected efferent arteriole is a common finding in association with diabetic glomerulosclerosis. As previously postulated, inasmuch as efferent arteriosclerosis may be assumed to raise intraglomerular pressure, and inasmuch as angiotonin is stated to produce hypertension by constriction of the efferent arteriole, the possible role of organic narrowing of efferent arterioles in the hypertension of elderly diabetics is sug-

PLATE 247. RENAL LESIONS IN DIABETES MELLITUS OTHER THAN  
DIABETIC GLOMERULOSCLEROSIS



FIG. A. Diabetic glomerulosclerosis in association with acute and chronic pyelonephritis. Diabetic glomerulosclerosis may be combined with a variety of renal lesions (A F I P Acc 71303)

FIG. B. Glycogen vacuolization of Armani-Elstein in the terminal portion of proximal convoluted tubules in a case of severe diabetes mellitus

tetrachloride

PLATE 248 · RENAL LESIONS IN DIABETES MELLITUS OTHER THAN  
DIABETIC GLOMERULOSCLEROSIS

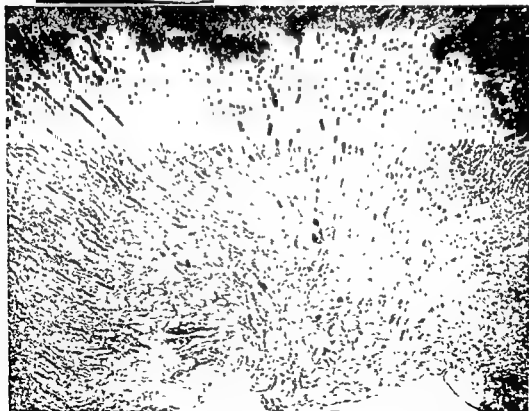


FIG. A. Necrotizing papillitis and hydronephrosis from a patient with diabetes mellitus and ureteral stenosis. (Courtesy Dr. W. A. D. Anderson, *Pathology*, C. V. Mosby.)

FIG. B. Necrotizing papillitis from a patient with diabetes mellitus. There is a bland ischemic, infarct-like necrosis of the papilla with a peripheral rim of leukocytes. Similar lesions have been produced experimentally with chemicals such as vinylamine and thall.



gested (Allen). Clearance studies in this connection might be of interest. Once again, however, the matter of limitations of the clearance studies must be raised. For example, it is noted that the elevated filtration fraction of 23 per cent, based on a study of one patient, has been interpreted as probably indicating increased constriction of the efferent arteriole (Rifkin et al.) Even if the resultant equivalence of constriction and the known organic narrowing of the efferent arterioles in diabetic glomerulosclerosis is allowed in deference to this interpretation, the effect of the multiple foci of "constriction" of the capillaries by diabetic glomerulosclerosis appears not to be included in the reckoning. Such stenosis of glomerular capillaries may conceivably raise intraglomerular tension as effectively as constriction of efferent arterioles. The hazards of the interpretation of the clearance studies is still further emphasized not only by the wide range of data but also by the disparity in the limited data inasmuch as other observers (Corcoran, Taylor and Page) noted a *diminished* rather than increased filtration fraction in patients with diabetic glomerulosclerosis. Both groups of investigators agree that there is a reduction in glomerular filtration rate and renal plasma flow. Twenty patients had urea clearances below 40 per cent (Rifkin).

5. Hyaline diabetic glomerulosclerosis shows no correlation with hyalinization of the pancreatic islets of Langerhans (Allen).

6. The marked dilatation of glomerular capillaries about the periphery of the lesions of diabetic glomerulosclerosis undoubtedly increases their permeability to proteins. It is suggested that this dilatation and permeability are responsible for the albuminuria which is one of the key disturbances of diabetic glomerulosclerosis (Allen). A similar histologic pattern occurs in glomerular amyloidosis and in lobular glomerulonephritis, in both of which conditions albuminuria is a pivotal disturbance.

7. Capillary lesions corresponding to the glomerular lesions are not present in other parts of the body of diabetic patients, including even gangrenous legs. Lesions simulating those of diabetic glomerulosclerosis occur in the retina,

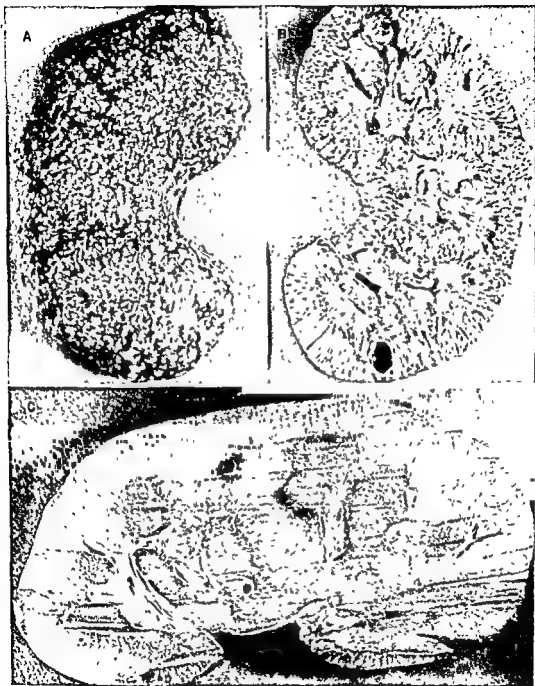
but, again, there are definite histologic differences.

8. Diabetic glomerulosclerosis represents sclerosis of the walls of the glomerular capillaries and not a sclerosis of the "mesangium" between them (Allen). The lesions of diabetic glomerulosclerosis are argyrophilic just as the basement membrane of normal capillaries and the argyrophilic Sclerosis of supporting stroma elsewhere does not result in a similar affinity for silver. The precise localization of the lesion to the vessel wall in contrast to supporting stroma is of obvious pathogenetic importance, especially in a disease such as diabetes mellitus in which generalized vascular sclerosis is the major unresolved problem.

#### *Other Renal Lesions in Diabetes Mellitus*

Other renal lesions occurring in patients with diabetes mellitus include: (1) glycogenic vacuolization of the loops of Henle (Armanni-Ebstein vacuoles) (plate 247B), (2) osmotic nephrosis, (3) fat nephrosis (plate 247C), and (4) necrotizing papillitis (plate 248).

1. Glycogenic vacuolization occurs in the kidneys particularly of uncontrolled diabetic patients, and except for the rare von Gierke's disease, and possibly de Toni-Fancconi's syndrome, is specific for diabetes mellitus. Whereas it was a common lesion in the preinsulin era (Warren), it has become an exceedingly infrequent finding. It is characterized by empty-appearing cells, the eosinophilic cytoplasmic granules of which have been replaced by fluid which is colorless with hematoxylin-eosin but stains as red granules with Best's carmine. The loops of Henle are involved almost exclusively. The nuclei are moderately pyknotic. No renal disturbance has been proved to result from these glycogenic deposits. Their relation to changes in the phosphatase content of the tubular epithelium remains to be demonstrated. This is mentioned for the patent reason that the transport of glucose across the tubular as well as intestinal epithelium is presumed to be dependent on the enzymatic hydrolysis of hexosephosphate. The explanation of the deposition of glycogen in the loops of Henle offered by Oliver (1950) is that the cells of the proximal portions of the nephron are "used" to handling glucose



FIGS. A AND B. *Amyloidosis of kidney with secondary contraction.* When hypertension is present with renal amyloidosis, this type of contracted kidney is likely to be found.

FIG. C. *Amyloidosis of kidney without contraction,* representing the more usual picture. The kidney is enlarged and firm, the resistance to cutting is reflected in the uneven marks produced by the knife.

whereas the cells of the loops of Henle are "unaccustomed" to contact with high concentrations of glucose and so polymerize the glucose to glycogen.

2 *Osmotic nephrosis*, as previously described (page 207; plates 106-110) consists of a fine tracery of vacuoles in the cells of the proximal tubules. These vacuoles may be produced with the administration of infusions of glucose apparently as a result of excessive concentrations of glucose in the proximal tubules. This oncotic condition appears to be reproduced in diabetic patients who spill glucose into the urine. Such vacuoles have frequently been mistaken for glycogen without the check of special stains. Actually they are hydropic and quite like those produced by hypertonic sucrose.

3 *Fat nephrosis* is described on page 218.

4. *Necrotizing papillitis* is discussed on page 348.

### RENAL AMYLOIDOSIS

The understanding of the available facts about renal amyloidosis has been somewhat clouded for several reasons. First, there is the confusion arising from the existence of the terms "para-amyloidosis" or "atypical amyloidosis." These terms refer to the occurrence of hyalinized, usually weakly, if at all, metachromatic, collagenous tissue present as sclerotic foci, or as actual palpable masses, in locations that would be atypical for ordinary amyloid. These locations include the skin, tongue, larynx, myocardium, articular and periarticular tissues, bone and cartilage; they rarely include the organs commonly involved in the

banal form of amyloidosis, namely, the kidney, liver, spleen, adrenal glands and intestine. The etiology of para-amyloidosis is unknown; it is the form generally found with multiple myeloma.

The typical form of amyloidosis is usually associated with chronic suppuration, as in tuberculosis, bronchiectasis, empyema, chronic abscesses and osteomyelitis, with a small percentage of various kinds of tumors, and with syphilis. In isolated instances, no apparently pathogenetically related disease is present. Experimentally, typical amyloidosis may be caused by the production of chronic suppuration or by the injection of various proteins, such as living or dead bacteria, toxins and casein or its sodium salt (Kuczynski; Jaffé). Amyloidosis may be developed in rabbits in 11 days (Krawkow), the time required for the production of human amyloidosis is usually a matter of months or years although periods as short as three weeks have been reported. Jaffé has increased the resistance to the occurrence of amyloidosis in mice with cholesterol feedings and, in some instances, with beef heart powder.

Second, confusion has arisen from the fact that the renal pathology has been pedagogically stuffed into the ill-fitting grab-bag of "nephrosis" and so the disease of the kidney has been called "amyloid nephrosis" with a consequent misdirection of attention to the renal tubules instead of the glomeruli. The result, once again, is that the attempt to explain the physiology of renal amyloidosis on this basis becomes awkward and forced since such an explanation is not predicated on the essential histologic change in the glomeruli.

amyloidosis, indicates that the patient had the clinical nephrotic syndrome

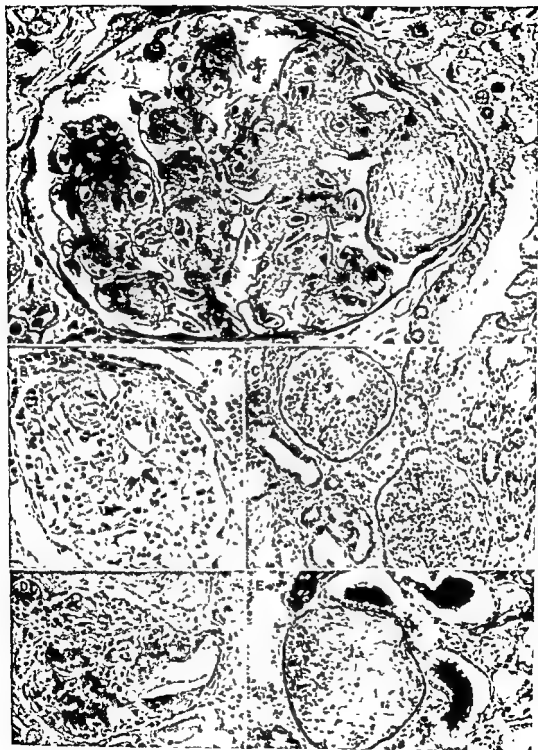
FIG. II. Glomerular amyloidosis showing origin within the capillary walls.

FIG. D. Glomerular amyloidosis illustrating partial amyloidotic conversion of the afferent arteriole. Note that the amyloid is not merely on the inner side but involves the full thickness of the wall, a feature that applies also to the capillaries, since they are extensions of the afferent arteriole.

FIG. C. Acute diffuse exudative glomerulonephritis combined with glomerular amyloidosis.

FIG. E. Dense casts in renal amyloidosis.

PLATE 250. AMYLOIDOSIS



(Legends on facing page)

PLATE 251. AMYLOIDOSIS



FIG A Diffuse glomerular amyloidosis

FIG B Amyloidosis of renal tubules and vessels

FIG C Amyloidosis of skin. This material stains metachromatically. Amyloid may be confined to the skin or may be part of a generalized amyloidosis. Cutaneous amyloidosis, however, is often part of para-amyloidosis or atypical amyloidosis

FIG D Experimental amyloidosis of rabbit. The fatty vacuolization of the proximal tubules corresponds to the picture in some of the amyloidotic kidneys in humans

PLATE 232. GENERALIZED ARTERIOLO-CAPILLARY THROMBONECROSIS  
WITH THROMBOPENIA

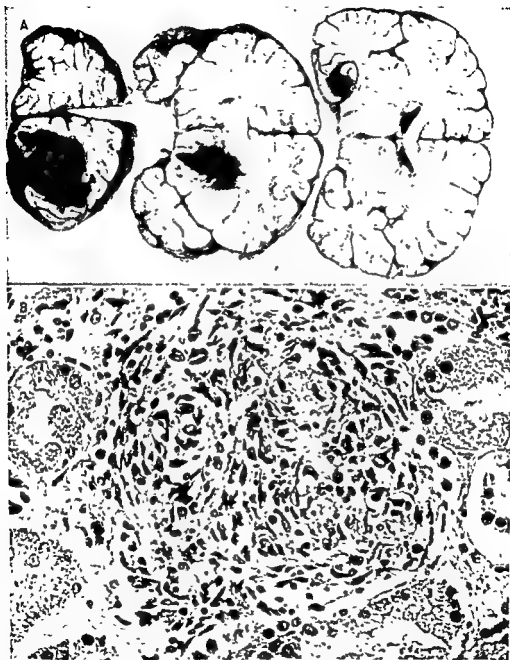


FIG. A. Massive cerebral hemorrhages in a case of generalized arteriolar and capillary thrombonecrosis. The cerebral hemorrhages are usually petechial in this disease.

FIG. B. Acute focal glomerulitis in a case of generalized thrombonecrosis. This lesion was present in very few of the glomeruli. Scattered granules of hemosiderin are in the epithelium of the proximal tubules.

### Clinical Picture

Renal amyloidosis may be entirely masked by the primary illness; it may result in mild urinary changes; or it may dominate the clinical picture. In any case of chronic suppuration, tuberculosis or old syphilis, amyloidosis should be considered. If in such a case, there is also a clinical picture of the nephrotic syndrome (that is, anasarca, hypoproteinemia, hypercholesterolemia, reversal of albumin-globulin ratio, and albuminuria) it is extremely likely that renal amyloidosis is present. The retention of the intravenously injected solution of the colloidal dye, Congo red, is practically diagnostic of amyloidosis. The Congo red test is usually normal in paramyloidosis. In amyloidosis, from 40 to 100 per cent of the dye leaves the blood stream within an hour to stain the amyloidotic tissue. Exceptionally, Congo red may disappear from the blood stream with abnormal rapidity in the absence of amyloidosis (Bennhold). Hypoproteinemia itself appears to be a factor in the rapid removal of Congo red.

Oliguria with high specific gravity of the urine usually occurs, as in other types of the nephrotic syndrome. Polyuria, occasionally marked, may be the first indication of amyloid disease. When associated with a low specific gravity, the polyuria is evidence of renal insufficiency, probably of the contracted variety of renal amyloidosis. The proteinuria, which tends to be variable, may be as great as 30 Gm. daily, an amount approaching the severest forms of chronic glomerulonephritis with edema ("lipoid nephrosis"). The loss of protein in the urine, as with other cases of protracted proteinuria, is probably the major factor in the accompanying hypoproteinemia, the reversal of the albumin-globulin ratio, and possibly also, by mechanisms as yet unknown, the hypercholesterolemia.

Relatively more globulin appears to be lost in renal amyloidosis than in the nephrotic syndrome due to other lesions (Geill). In one case the blood cholesterol reached a level of 920 mg per cent (Linder et al.). Fishberg points out that the cachexia which may accompany amyloidosis may interfere with an anticipated elevation in the cholesterol level. Similarly, cachectic edema may occur and be mistaken for edema of renal origin. The involvement of the liver with amyloid may also lead to hypoproteinemia and edema, which may be mistakenly attributed to the kidneys.

*Casts* in the urine are of the hyaline, granular, waxy and epithelial variety but they are relatively few in number. Doubly refractile bodies, debris and cells, are commonly found in the urine just as they are in the urine in patients with the nephrotic syndrome of diabetic glomerulosclerosis or chronic glomerulonephritis. Pyuria and hematuria are not present as a rule.

*Azotemia* as a result of renal amyloidosis occurs infrequently, and may be absent even with extensive glomerular amyloidosis. Only 40 cases of renal amyloidosis and associated hypertension have been recorded in the literature (Leard and Jaques), most of these were instances of contracted amyloidotic kidneys.

*Disappearance of amyloidosis* has been reported in mice (Kuczynski) and, in rare instances, in man (Reimann).

### Pathology

#### Gross appearance

Typically the kidneys with extensive amyloidosis are diffusely enlarged to about one and one half times normal size; in extreme cases each kidney may weigh over 400 Gm. The capsule is easily stripped over a smooth yellow-brown surface. In the process of cutting the kid-

FIG A Generalized arteriolo-capillary thrombocrosis involving the kidneys

FIG B Interlobular arteritis with thrombosis, marked endothelial hyperplasia, and luminal dilatation. The associated glomerulus is not remarkable

FIGS C AND D Interlobular arteritis and thrombosis with focal fibrinoid degeneration from a case of fulminant thrombopenia, purpura and death in several weeks. The markedly dilated vessel contains a thrombus. The glomerulus shows slight increase in cellularity. Hemosiderin granules, . . .

PLATE 253. GENERALIZED ARTERIOLO-CAPILLARY THROMBOSIS  
WITH THROMBOPENIA



(Legends on facing page)



PLATE 234.—GENERALIZED ARTERIOLO-CAPILLARY THROMBONECROSIS  
WITH THROMBOPENIA

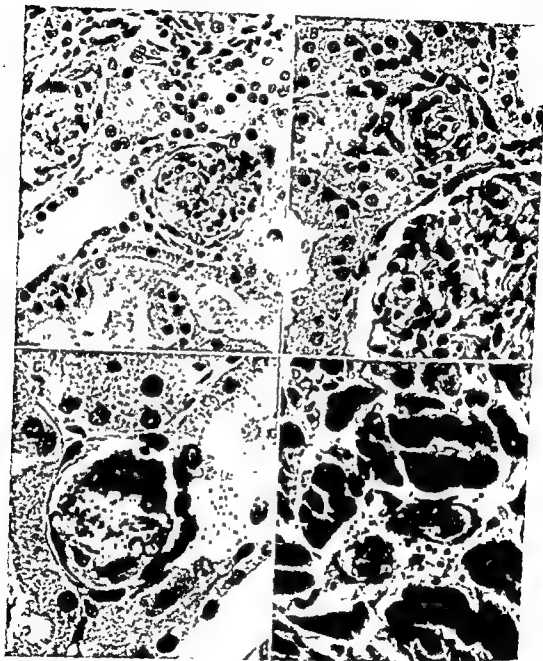


FIG A Smudgy homogenous fibrinoid necrosis of portions of the afferent arteriole is evident

FIG C Fibrinoid necrosis with hyperchromatism of cells of the arteriole is noted in this partially thrombosed vessel

FIG B Distinct thickening with focal, obviously intramural fibrinoid degeneration is noted in this afferent arteriole

FIG D Arteriolocapillary thrombonecrosis of the myocardium The necrosis of vessel walls appears to be the starting point of the platelet-like verruca originating and developing directly in the wall

ney, the knife meets a characteristic tough resistance that, by itself, suggests the diagnosis (plate 249). On inspection the sectioned surface resembles that of the large "white" kidney of chronic membranous or lobular glomerulonephritis ("lipoid nephrosis") because of the yellow-brown or ochre color, the widened cortex, and the tough waxy consistency. The tan cortex and brown medulla are fairly sharply demarcated. The glomeruli are visible by oblique light as enlarged, greyish, translucent appearing dots. The vessels are not remarkable grossly. The application of Lugol's solution after dilute acetic acid reveals a dark brown stain at the sites of amyloid deposition.

Infrequently the kidneys with amyloidosis have granular rather than "smooth" surfaces (plate 249A, B). These represent the "contracted" kidneys which, despite the scarring, rarely weigh or measure less than normal presumably because of the compensatory increase of the fatty tubules and edematous interstitium. An analogous situation obtains in the case of diabetic glomerulosclerosis.

### *Histologic appearance*

**Glomeruli.** The glomeruli are the site of principal change when the full-blown picture of the nephrotic syndrome is present. The glomerular tuft is converted into multiple, homogeneously pink (hematoxylin-eosin) spheres, closely simulating the lesions of diabetic glomerulosclerosis (plate 250). The spheres take the metachromatic stains for amyloid (e.g., Congo red, crystal violet). The amyloidotic material represents a nodular conversion of the walls of the glomerular capillaries rather than a deposit of a substance on their luminal aspect or in the intercapillary tissue. This feature of the lesion can be traced not only in serial sections but also in a single section in which the initial stages of amyloidotic thickening of the capillary walls are evident (plate 250). In other words, the amyloidosis represents an *in situ* conversion of pre-existing reticulin or collagen, rather than an accretion of material deposited on the inner aspect of a basement membrane. The distinction clearly is of pathogenetic importance.

There is some tendency for the peripheral capillaries to be dilated about the hyaline

spheres but this feature, as well as the layering of nuclei at the rim of the spheres is not nearly as marked as in diabetic glomerulosclerosis. Moreover, the spheres are usually not quite as sharply circumscribed as the diabetic lesion. In further contrast, the amyloid spheres of the glomeruli are often marked by artefactual linear streaks reflecting the different densities of the two lesions (plate 245A). When a single glomerular sphere is present in diabetic glomerulosclerosis, it is likely to be situated opposite the vascular pole, there is no such tendency in glomerular amyloidosis. The differential pattern with the silver stain is striking (plate 243, 244). Finally, the efferent arteriole is commonly thickened in association with diabetic glomerulosclerosis but is infrequently involved with amyloidosis (plate 241E, F).

The very early stages of glomerular amyloidosis may be mistaken in routine stain (hematoxylin-eosin) for the capillary sclerosis of benign nephrosclerosis. However, in the early glomerular amyloidosis, the thickened capillary walls have a soft, almost smudgy, rather than dense, appearance of benign nephrosclerosis.

**Vessels.** The amyloidosis tends to involve the smaller renal vessels, especially the afferent arterioles, interlobular arteries, and arcuate arteries. The afferent arterioles may be markedly dilated and thickened at the hilum (plate 250D). The media particularly, but also the intima and even the adventitia of the larger vessels may be involved. Amyloidosis may also involve the interstitial collagen abundantly.

**Tubules.** The tubules in a given kidney may show one or all of the following changes:

- 1 Fatty vacuolization of the epithelium of the proximal tubules (plate 251D). Much of the fat is anisotropic as in the tubules of diabetic glomerulosclerosis, and chronic lobular or membranous glomerulonephritis. This tubular change occurs when there is extensive glomerular amyloidosis along with the clinical nephrotic complex.
- 2 Amyloid thickening of the tubular basement membrane (plate 251B) which may reach an extreme degree.
- 3 Dense hyaline casts in the distal convoluted tubules (plate 250E) and below. It is prob-

PLATE 255. SHOCK: INTRAGLOMERULAR CAPILLARY THROMBOSIS



FIG A Intraglomerular capillary thrombosis with small early infarction in shock. The necrosis of the epithelium of the more vulnerable proximal tubules is evident in contrast to the better preserved epithelium of the pale staining distal tubules. Droplets of fat in the tubular epithelium may occur in shock.

FIG B Intraglomerular capillary thrombosis in shock and dehydration.

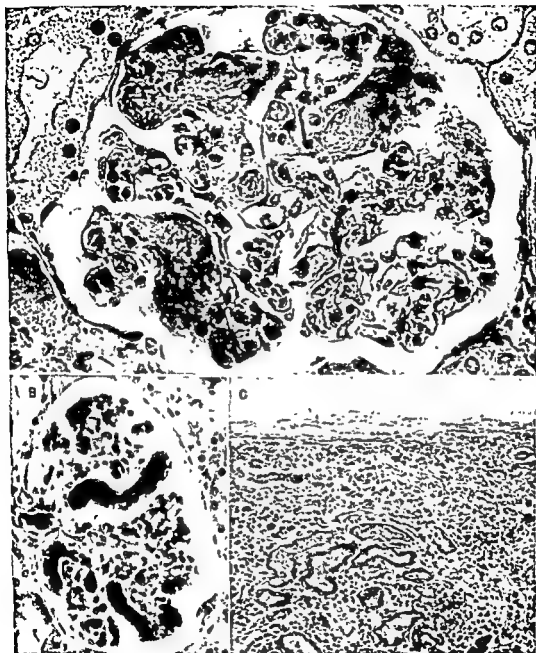


FIG. A High magnification of capillary thrombosis in shock with dehydration: the thrombotic material resembles fibrin but it is, in reality, packed, partially laked, red blood cells.

FIG. B Glomerular capillary thrombosis occurring in shock associated with dehydration.

FIG. C Renal infarct in shock without associated vascular thrombosis. The necrosis is the result of ischemia from local diversion of the flow of blood.

able that these dense obstructive casts are in considerable measure responsible for a large proportion of the tubular atrophy.

4. Much of the tubular atrophy appears analogous to the atrophy secondary to the dense casts in the kidney in multiple myeloma. Glomerular amyloidosis and narrowing of arteries and arterioles by the amyloidosis also must contribute in some part to the tubular atrophy. As far as the glomerular contribution is concerned, it is curious that in some cases with extreme glomerular involvement, the tubules may show no significant atrophy. This disparity between the degree of the glomerular and tubular involvement may occur also in acute glomerulonephritis.

5. Conspicuous hyaline granules, or hyaline droplets are seen in the epithelium of the convoluted tubules. For reasons discussed in the section under "Hyaline Granule Nephrosis," these are regarded as an intrinsic cytoplasmic alteration rather than as granules of protein reabsorbed from the tubular lumen.

The kidneys are rarely the only organs involved by amyloidosis, on the other hand, the liver and spleen are frequently the sites of amyloidosis to the exclusion of the kidney.

#### GENERALIZED ARTERIOLE-CAPILLARY THROMBONECROSIS

##### Introduction

In recent years there has been renewed interest in the disease first described by Moschkowitz in 1923, by 1948, 71 cases had been reported. The lesion is uncommon but not as rare as this small number of reports indicates. The diagnosis is almost never made clinically and has often been missed on histologic examination. The disease is characterized by a sudden onset of purpura, fever, thrombocytopenia, ane-

mia and of an urticarial or other rash in about 25 per cent of cases. Hepatomegaly and splenomegaly occur occasionally. Headache, convulsions, delirium, coma, focal paresis and hemiplegias may accompany the picture. The course of the disease leads to death in from one to seven weeks. No age group is selectively involved, the reported range being from 9 to 66 years (Adams et al.). Clinically, the entire group of purpuras, and especially Werlhof's purpura, enters into the problem of differential diagnosis. The lack of a favorable response to transfusions separates this disease from Lederer's anemia with which it is initially linked.

##### Pathology

##### Gross appearance

Grossly, the essential changes are the effects of purpura. The prominent neurologic manifestations are also the result of the hemorrhagic diathesis although in only one case were massive cerebral hemorrhages demonstrated (plate 252A).

##### Histologic appearance

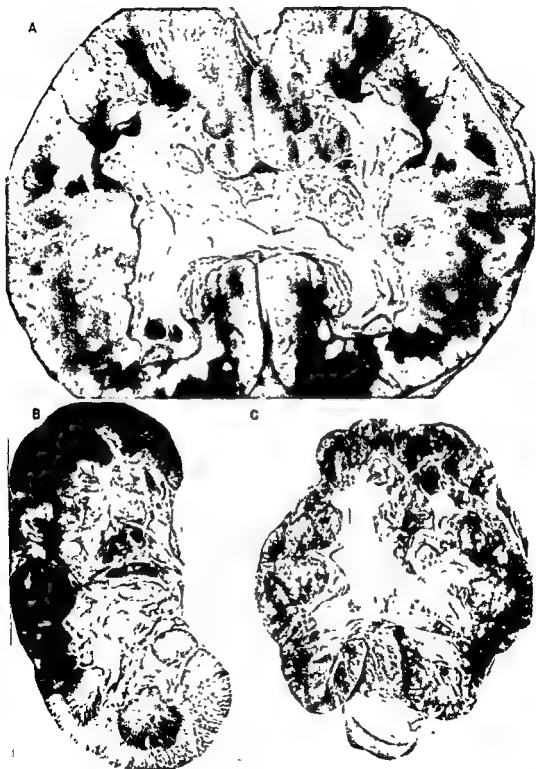
The essential histologic change involves the small arteries, arterioles, and capillaries in every organ of the body. Veins are not involved although some of the arterioles may be so dilated as to resemble veins. The organs with the fewest vessels involved are the lungs, a feature common also to other diffuse vascular diseases. The lumen of the vessels is occupied by a granular, eosinophilic material which projects eccentrically into the lumen from one segment of the wall (plate 253, 254). These "thrombi" do not entirely occlude the lumen but usually leave an irregular crescent of free space between their periphery and the intima. As a rule, the periphery of the thrombi is lined by freshly proliferated endothelial cells which may

FIG. A Massive ischemic infarction of kidney due to embolus in renal artery from a mural thrombus in the heart

FIG. B Renal ischemic infarct due to embolus to arcuate artery. The zone immediately subcapsular is spared the necrosis, apparently because of collateral capsular circulation.

FIG. C Remarkable case of unilateral cortical necrosis in which thrombosis was present only in the sclerotic renal artery of otherwise negative contralateral kidney. Other photographs from this case are in plates 225 and 226.

PLATE 237. ISCHEMIC (ARTERIAL) INFARCT



(Legends on facing page)



FIG. A *Acute renal infarct due to embolus to artery.* The epithelium of the distal convoluted tubules is better preserved than the epithelium of the proximal tubules which, as shown here, are completely necrotic.

FIG. B *Recent infarct due to embolus to renal artery.* Much leukocytic reaction and hemorrhage are present.

FIG. C *Acute renal infarct in periaortic nodosa.* The leukocytic infiltrate is a reaction to the infarction and not of periaortic nodosa.



FIG. A. Mycotic (embolic) renal arteritis with thrombosis and aneurysmal dilatation in a case of bacterial endocarditis. No infarct was present.

FIG. B. Mycotic acute arteritis. If such a lesion would resemble the end result of py...

FIG. C. Medullary infarct in a nondiabetic, simulating necrotizing papillitis. Under cases of necrotizing papillitis are filed as well as simple medullary infarcts.



also canalize a portion of the "thrombi." The endothelial cells or fibroblasts may be so numerous as to form a cellular mass and obscure the lesion (plate 253D).

The vessels themselves, especially the afferent arterioles, may be so dilated as to be mistaken for venules or even tubules (plate 253B, C). Serial sections of these vessels invariably reveal a focus of fibrinoid swelling in a segment of their walls and it is usually at this site that the "thrombus" is initiated (plate 254). This same type of fibrinoid damage may be seen in its early stages as a mural hillock of fibrinoid degeneration without attached "thrombi," as demonstrated in serial sections (plate 254). This is the essential quality and pattern of change observed in other sites in this condition, and in other diseases, as in the typhus fevers (Allen and Spitz), and in the valvular changes of endocardiosis, rheumatic valvulitis, bacterial endocarditis and Libman-Sacks endocarditis (Allen and Sirota). In these latter instances, intrinsic fibrinoid changes directly in the collagen of vessels and valves with internal exudation of plasma into their walls simulate external accretion of thrombi from the lumen. In the case of the generalized vascular "thrombosis," the material in the lumen can not be unequivocally distinguished from platelet thrombi by current histologic methods although some observers (Engel et al.) call attention to tinctorial discrepancies between these "thrombi" and unquestionable platelet thrombi. The impression gained by us is that these "thrombi" actually represent clotted and partially organized plasma which has been exuded into the lumen from that portion of the vascular wall which has undergone fibrinoid swelling. In other words, the disease appears to be primarily a diffuse vascular disease in much the same sense that periarteritis nodosa is. In this connection, it is of interest that many patients with this acute disease, that is, generalized arteriolo-capillary thrombocytopenia, have a history of allergy with urticaria. The thrombocytopenia might better be related, however nebulously at present, to some such factor as allergy or toxicity, rather than to the withdrawing of platelets from the peripheral blood to form the "thrombi," a mechanistic theory suggested

originally by Klemperer, Bachr and Schifrin. After all, if all of these thrombi were packed together, there is no arithmetical reason to believe that they would outnumber the platelets that go into the formation of some huge blood clots unassociated with thrombopenia. On the other hand, the association of allergy and thrombopenia is a long recognized phenomenon.

The bone marrow shows no specific qualitative change in its cellular elements, including the megakaryocytes, the latter may be somewhat increased. However, the vascular lesions occur also in the marrow and a biopsy could be the source of an antemortem diagnosis (Fitzgerald et al.)

### SHOCK

Several varieties of renal lesions have either a direct or intermediate pathogenetic relationship to shock. These are:

Diffuse glomerular thrombosis.

Intrarenal venous thrombosis.

Fatty degeneration or necrosis of proximal tubular epithelium.

Hemoglobinuric ("lower nephron") nephrosis.

Renal infarction.

Isolated.

Bilateral cortical necrosis.

### Diffuse Glomerular Thrombosis

There occurs in shock, particularly when associated with severe dehydration, a form of diffuse thrombosis of the glomerular capillaries. The thromboses may involve a few peritubular capillaries, but they are practically confined to the glomeruli (plate 255, 256). Organs other than the kidney are not affected. Thrombi are occasionally fibrinous, but more often they merely simulate fibrin and are in reality freshly clumped masses of erythrocytes which have provoked no other glomerular histologic reaction (plate 256A). The lesions are obviously preagonal and are not responsible for renal insufficiency of more than several hours' duration, if at all. These thromboses have been observed not only in nonspecifically shocked, dehydrated patients, but also in carbon monoxide poisoning and in plague (Ash and Spitz) (plate 159B). The lesion is not to be confused with the



FIG. A Old infarcts of kidney due to emboli of renal arteries. The depth and irregularity of the scars of infarction are illustrated.

FIGS. B AND C Organized infarcts of kidney due to embolism from cardiac mural thrombi. The depth of the depression is to be contrasted with the shallow scars of pyelonephritis.

FIGS. D AND E Old and recent infarcts of varying ages.

PLATE 261. ISCHEMIC (ARTERIAL) INFARCT

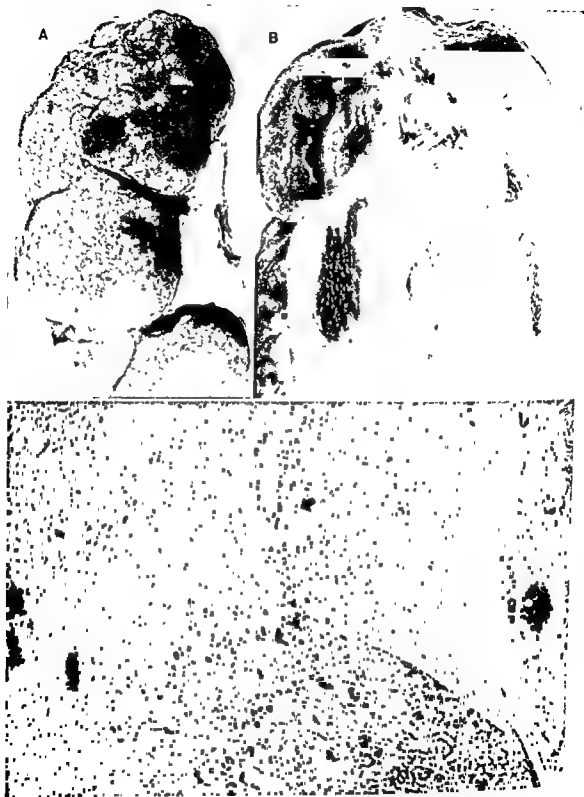


FIG A Distortion of renal surface due to old arterial infarcts

FIG B Recent and old arterial infarcts due to embolism from cardiac mural thrombi.

FIG C Healed renal infarct demonstrating cortical depression, the hyalinized glomeruli (arrow), and the overlying, thickened, adherent vascularized capsule



FIG. A Old infarct showing cortical depression at site of scarred atrophic parenchyma

FIG. B Fibrotic glomeruli, partially or completely resorbed at the periphery of an infarct

FIG. C Compressed cluster of atrophic hyalinized glomeruli in the scar of an old infarct

occurrence of thrombosis in isolated capillaries in acute diffuse glomerulonephritis, in eclampsia, in malignant nephrosclerosis, in diffuse arteriolocapillary thrombocrosis with thrombocytopenia, or with the verrucal capillary thickenings of the glomeruli in disseminated lupus erythematosus. One of the puzzling features of this lesion of glomerular thrombosis is its relatively infrequent occurrence.

Of the remainder of the renal lesions in which shock is presumed to participate, hemoglobinuric ("lower nephron") nephrosis, and bilateral cortical necrosis are of chief concern. These are discussed in detail separately. Focal fatty degeneration of the proximal tubular epithelium is common but is not clinically important. Intrarenal venous thrombosis in shock is neither common nor of apparent importance (plate 263); necrosis of proximal tubular epithelium is also an infrequent manifestation of shock but it may be functionally significant when it does occur. Isolated renal infarction as a result of shock is another unusual effect in humans (plate 250C).

### RENAL INFARCTS

Renal infarcts are produced by one of three basic hemodynamic mechanisms:

#### Arterial

Embolism

Thrombosis

Organic narrowing

Functional—shock

Venous (thrombosis)

Infarcts are of three kinds: (1) ischemic, (2) hemorrhagic, and (3) combined. Arterial and functional infarcts are ischemic, venous infarcts are always hemorrhagic. Occasionally there appear to be combined infarcts with both ischemic and hemorrhagic necrosis. These usually are primarily ischemic infarcts with superimposed hemorrhagic admixture because of diapedesis, necrosis of walls of vessels, and secondary venous stasis and thrombosis in the smaller vessels. This hemorrhagic reaction secondary to ischemic infarction is observed also in other organs, as, for example, in myocardial infarct. In some instances, however, combined infarcts are caused by simultaneous thrombosis of artery and vein.

### *Clinical Picture of Renal Infarcts*

The signs and symptoms of renal infarcts are local pain, tenderness in the flank, shock, hematuria, and albuminuria. The pain lasts from one week to ten days. A sudden rise of blood pressure, sustained over weeks, may occur as a result of the infarction. In venous infarction, the kidney may become so engorged as to be palpable. The retrograde pyelogram may or may not show some alteration. Function of the affected kidney is likely to be diminished or totally absent, depending on the size of the involved area. The clinical diagnosis of renal infarction is generally overlooked. The signs and symptoms of renal infarction may be mistaken for splenic infarction, renal neoplasm, paranephric abscess, essential hematuria, renal calculus, or a ruptured viscus.

### *Pathology of Renal Infarcts*

The acute ischemic infarct is characteristically wedge-shaped, with the base of the triangle at the capsule, yellow to yellowish grey, and usually with a hemorrhagic border (plates 257, 260, 261). Several isolated infarcts may occur in the same kidney or the individual infarcts may coalesce to the extent of being indistinguishable from cortical necrosis of the kidney. This similarity leads to noting that very often the necrosis is confined to the cortex and spares the medulla, as it generally does in bilateral cortical necrosis (plate 230A).

In the *healed state*, the infarcted area appears as a deeply depressed area with the capsule usually increased in thickness, highly vascularized, and strongly adherent to the cortex in the area of infarction (plate 261). The altered appertaining artery leading to the area may be identified in many instances. The scar of the infarct may become irregularly calcified. Occasionally, the residuum of an old infarct is cystic, secondary to liquefaction degeneration of the infarcted tissue in the early stage.

The *hemorrhagic infarct* almost always takes the form of hemorrhagic necrosis of the entire kidney, such as occurs particularly in the newborn, after thrombosis of the renal vein.

Histologically, there is little to record about the nature of the infarcts that is not more adequately illustrated in the photomicrographs.

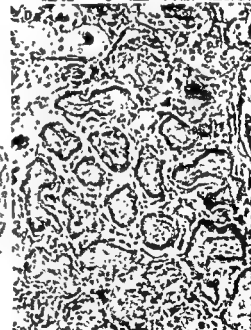
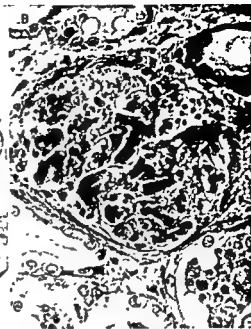


FIG. A. Acute thrombosis of several days' duration of renal veins and their small tributaries. No renal infarcts were present. The kidneys were not insufficient.

FIG. C. Thrombosis of renal vein following spleno-renal venous anastomosis for cirrhosis. The renal parenchyma showed no noteworthy changes.

FIG. B. Thrombosis of glomerular capillaries following thrombosis of renal veins (from kidney of figure A).

FIG. D. Small infarct following thrombosis of small tributary of renal vein in an adult.

occurrence of thrombosis in isolated capillaries in acute diffuse glomerulonephritis, in eclampsia, in malignant nephrosclerosis, in diffuse arteriolocapillary thrombocrosis with thrombocytopenia, or with the verrucal capillary thickenings of the glomeruli in disseminated lupus erythematosus. One of the puzzling features of this lesion of glomerular thrombosis is its relatively infrequent occurrence.

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Infarcts are of three kinds: (1) ischemic, (2) hemorrhagic, and (3) combined. Arterial and functional infarcts are ischemic, venous infarcts are always hemorrhagic. Occasionally there appear to be combined infarcts with both ischemic and hemorrhagic necrosis. These usually are primarily ischemic infarcts with superimposed hemorrhagic admixture because of diapedesis, necrosis of walls of vessels, and secondary venous stasis and thrombosis in the smaller vessels. This hemorrhagic reaction secondary to ischemic infarction is observed also in other organs, as, for example, in a myocardial infarct. In some instances, however, combined infarcts are caused by simultaneous thrombosis of artery and vein.

#### Clinical Picture of Renal Infarcts

The signs and symptoms of renal infarcts are local pain, tenderness in the flank, shock, hematuria, and albuminuria. The pain lasts from one week to ten days. A sudden rise of blood pressure, sustained over weeks, may occur as a result of the infarction. In venous infarction, the kidney may become so engorged as to be palpable. The retrograde pyelogram may or may not show some alteration. Function of the affected kidney is likely to be diminished or totally absent, depending on the size of the involved area. The clinical diagnosis of renal infarction is generally overlooked. The signs and symptoms of renal infarction may be mistaken for splenic infarction, renal neoplasm, paranephric abscess, essential hematuria, renal calculus, or a ruptured viscus.

#### Pathology of Renal Infarcts

The acute ischemic infarct is characteristically wedge-shaped, with the base of the triangle at the capsule, yellow to yellowish grey, and usually with a hemorrhagic border (plates 257, 260, 261). Several isolated infarcts may occur in the same kidney or the individual infarcts may coalesce to the extent of being indistinguishable from cortical necrosis of the kidney. This similarity leads to noting that very often the necrosis is confined to the cortex and spares the medulla, as it generally does in bilateral cortical necrosis (plate 230A).

In the *healed state*, the infarcted area appears as a deeply depressed area with the capsule usually increased in thickness, highly vascularized, and strongly adherent to the cortex in the area of infarction (plate 261). The altered appertaining artery leading to the area may be identified in many instances. The scar of the infarct may become irregularly calcified. Occasionally, the residuum of an old infarct is cystic, secondary to liquefaction degeneration of the infarcted tissue in the early stage.

The *hemorrhagic infarct* almost always takes the form of hemorrhagic necrosis of the entire kidney, such as occurs particularly in the newborn, after thrombosis of the renal vein.

Histologically, there is little to record about the nature of the infarcts that is not more adequately illustrated in the photomicrographs.

PLATE 23. ACUTE THROMBOSIS OF RENAL VEINS

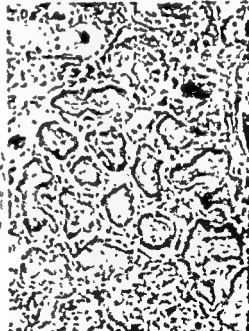
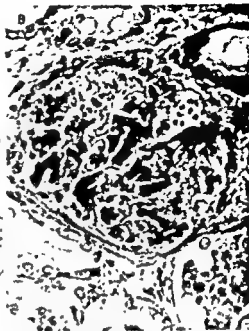


FIG. A. Acute thrombosis of renal vein. Occlusion of lumen and their usual infiltration. No renal infarct was present. The thrombus was not stained.

FIG. C. Thrombosis of renal vein following pyelonephritis. Acute thrombosis of renal vein. The renal parenchyma was not stained with changes.

FIG. B. Thrombosis of renal vein. Occlusion of lumen and their usual infiltration. No renal infarct was present.

FIG. D. Acute thrombosis of renal vein. Occlusion of lumen and their usual infiltration.



occurrence of thrombosis in isolated capillaries in acute diffuse glomerulonephritis, in eclampsia, in malignant nephrosclerosis, in diffuse arteriolocapillary thrombonecrosis with thrombocytopenia, or with the verrucal capillary thickenings of the glomeruli in disseminated lupus erythematosus. One of the puzzling features of this lesion of glomerular thrombosis is its relatively infrequent occurrence.

Of the remainder of the renal lesions in which shock is presumed to participate, hemoglobinuric ("lower nephron") nephrosis, and bilateral cortical necrosis are of chief concern. These are discussed in detail separately. Focal fatty degeneration of the proximal tubular epithelium is common but is not clinically important. Intrarenal venous thrombosis in shock is neither common nor of apparent importance (plate 263), necrosis of proximal tubular epithelium is also an infrequent manifestation of shock but it may be functionally significant when it does occur. Isolated renal infarction as a result of shock is another unusual effect in humans (plate 256C).

### RENAL INFARCTS

Renal infarcts are produced by one of three basic hemodynamic mechanisms:

#### Arterial

Embolism

Thrombosis

Organic narrowing

Functional—shock

#### Venous (thrombosis)

Infarcts are of three kinds: (1) ischemic, (2) hemorrhagic, and (3) combined. Arterial and functional infarcts are ischemic, venous infarcts are always hemorrhagic. Occasionally there appear to be combined infarcts with both ischemic and hemorrhagic necrosis. These usually are primarily ischemic infarcts with superimposed hemorrhagic admixture because of diapedesis, necrosis of walls of vessels, and secondary venous stasis and thrombosis in the smaller vessels. This hemorrhagic reaction secondary to ischemic infarction is observed also in other organs, as, for example, in a myocardial infarct. In some instances, however, combined infarcts are caused by simultaneous thrombosis of artery and vein.

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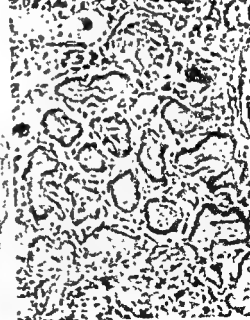
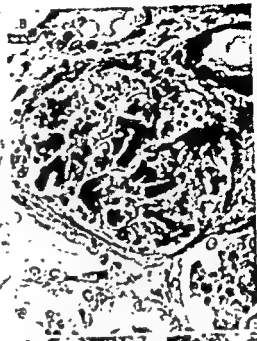


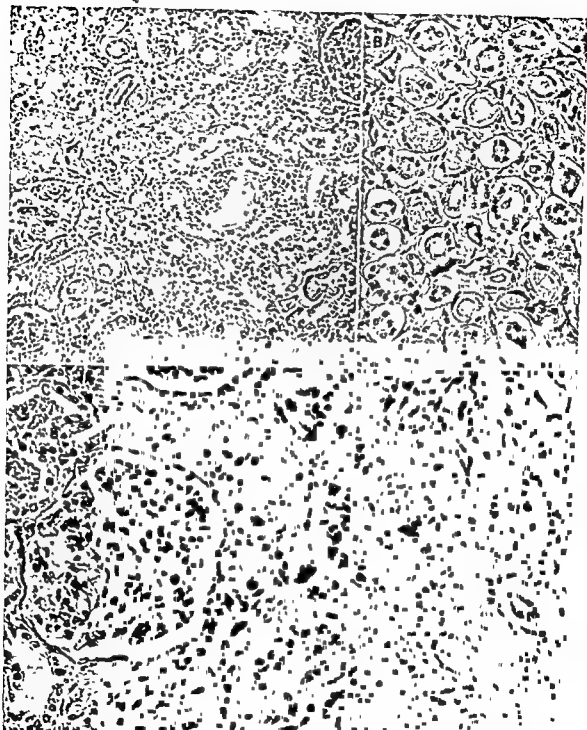
Fig. A. Gross thrombosis of renal vein, section of renal vein and there great tributaries. No renal infarcts were present. The kidneys were not much atax.

Fig. B. Thrombosis of primary renal vein, section of renal vein and there great tributaries of figure A.

Fig. C. Thrombosis of renal vein, section of renal vein and there great tributaries. The renal infarcts were not much atax. The renal infarcts were not much atax.

Fig. D. Section of renal vein, section of renal vein and there great tributaries of figure A.

PLATE 264. CHRONIC THROMBOSIS OF RENAL VEINS



These photomicrographs show the relatively mild changes in renal parenchyma following long standing thrombosis of main renal veins with an associated clinical syndrome simulating lipid nephrosis. Scattered slight interstitial fibrosis, tubular degeneration and protein casts are noted.

PLATE 26 CHRONIC THROMBOSIS OF RENAL VEINS

[illegible]

(plates 258, 261C, 262) The ischemic infarcts in the early stages are often rimmed by leukocytic as well as hemorrhagic borders (plate 258B, C). Evidence of regeneration, particularly of the proximal tubular epithelium, may be seen very early. The distal convoluted tubules may be viable in the midst of more vulnerable necrotic proximal tubules (plate 258A). Septic infarcts may contain purulent exudate throughout the area of necrosis. The healed stages are identified by the masses of closely packed hyalinized fibrotic residues of glomeruli and scar tissue in an indented wedged area with adherent capsular and pericapsular vascular scar (plates 261C, 262C) Necrotizing papillitis is occasionally regarded as a medullary infarct (plate 259C).

#### *Etiology of Arterial Infarcts*

Most of the arterial infarcts are caused by embolism from cardiac mural thrombi complicating myocardial infarctions, and from vegetations of subacute bacterial endocarditis. Infrequently, emboli from verrucal endocarditis, and atheromatous plaques or mural thrombi of the aorta may reach the kidney. Infarcts due to thrombosis of the renal artery are the result principally of periarteritis nodosa and mycotic arteritis. Thrombosis of the renal artery occurs also secondary to sclerotic narrowing and rarely from thromboangitis obliterans and syphilitic endarteritis. Arterial infarcts may follow marked narrowing of renal arteries or their branches as a result of sclerosis or periarteritis nodosa, for example, without actual thrombotic occlusion. The mechanism in these instances is renal arterial insufficiency and the infarcts are not necessarily ever acute but rather may be of the torpidly progressive ischemic type that is commonly seen in the kidneys with marked arteriosclerosis. In addition, acute infarcts on a functional basis may occur in shock (Penner and Bernheim), or as a result of the action of certain poisons or drugs. The ultimate example of infarction on a functional basis is bilateral cortical necrosis (plate 266). A remarkable example of functional infarction is illustrated in plates 225 and 226. In this case, which was cited previously in regard to the pathogenesis of hypertension (page 412), thrombosis of a

sclerotic left renal artery occurred in a hypertensive white male, 52 years of age; despite the thrombosis, the parenchyma of this kidney was not altered, but cortical necrosis occurred in the opposite right kidney. The right kidney showed prominent arteriosclerosis and intrarenal arteriosclerosis in sharp distinction from the left kidney in which only the extraparenchymal renal arteries were sclerotic, thus behaving in effect as a Goldblatt clamp.

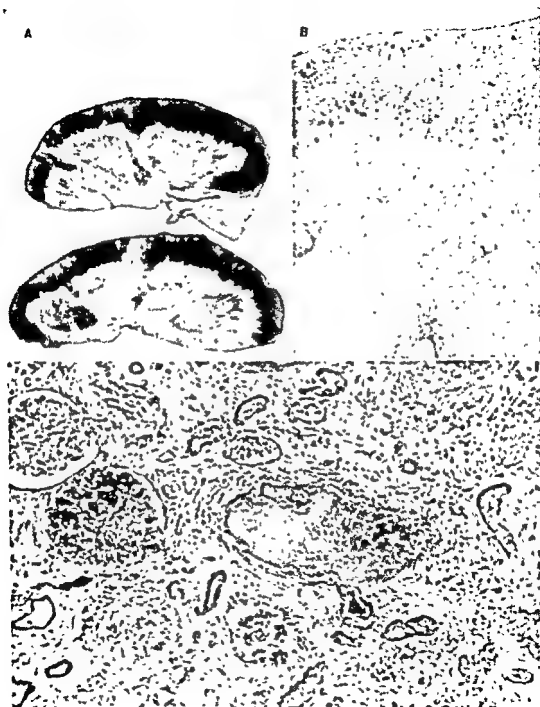
Occasionally, the main renal artery appears completely occluded by thrombosis without apparent destruction of the parenchyma, as in the case just cited, or with only mild atrophy of the kidney as illustrated in plate 227. The explanation must reside in the presence of adequate but not always evident collateral circulation.

#### *Thrombosis of Renal Veins*

The effect of thrombosis of the main renal vein is generally although not always different in adults and infants.

In infants, particularly newborn infants, thrombosis of the main renal arteries is associated with a massive hemorrhagic infarction of the kidneys. This type of infarction has been observed in infants, especially those with severe diarrheal diseases and marked dehydration. Although previously considered to be rare, total hemorrhagic renal infarctions were observed in 4 of 25 autopsied cases of infants with severe epidemic diarrhea (Barenburg et al.). In two of these, the infarction was accompanied by thrombosis of the main renal vein; in the other two, the veins were not involved. When present, the thrombus is generally confined to the main renal vein. In the case of Marshall and Whapham, bilateral massive hemorrhagic infarction was noted in a newborn infant in the absence of thrombosis of the main renal veins. In this case there was no diarrhea or apparent infection. In 7 of 8 clearly documented cases of hemorrhagic infarction of the kidney collected from the literature by Regan and Crabtree, the patients were infants and thrombosis of the main renal veins occurred in each. The associated diseases were gastroenteritis in 4, lobular pneumonia in 1, and cellulitis extending from an abscess of the groin in 1. The ages of these 6 patients (5 males,

PLATE 29. ARTIFICIAL AND ARTIFICIAL-INDUCED BRUTAL  
OPTICAL NUCLEUS



(plates 258, 261C, 262). The ischemic infarcts in the early stages are often rimmed by leukocytic as well as hemorrhagic borders (plate 258B, C). *Evidence of regeneration*, particularly of the proximal tubular epithelium, may be seen very early. The distal convoluted tubules may be viable in the midst of more vulnerable necrotic proximal tubules (plate 258A). Septic infarcts may contain purulent exudate throughout the area of necrosis. The healed stages are identified by the masses of closely packed hyalinized fibrotic residues of glomeruli and scar tissue in an indented wedged area with adherent capsular and pericapsular vascular scar (plates 261C, 262C). Necrotizing papillitis is occasionally regarded as a medullary infarct (plate 259C).

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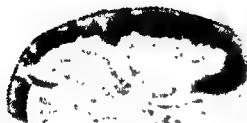
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21

70



1 female) were 9 days (Heller), 13 and 29 days (Campbell and Matthews), 2 months (Aschner), 3 months (Gruneberg), and 2 years (Fuhr). Three of these infants survived nephrectomy. The two other cases were in adults aged 20 years (Danhez) and 33 years (Melick and Vitt), who developed the infarction apparently 5 days and 65 days postpartum respectively. In one case, recently reported, the mother of a 7 day old infant had had a toxemia of pregnancy (Cabot case 36032). In this case there was anuria from the time of birth and azotemia up to a level of 220 mg per cent (NPN). Hemorrhagic infarction occurred in only one of the kidneys—the one with the thrombosis of the main renal vein—but intrarenal venous thromboses were present in both kidneys. Bilateral total hemorrhagic infarctions of the kidneys are, of course, invariably fatal. The patient with unilateral massive hemorrhagic infarction may occasionally be saved by prompt nephrectomy.

The cases of hemorrhagic infarction occurring without thrombosis of the renal veins raise the possibility that when such thrombosis is present, it is secondary to the infarction, or, at least, not the cause of it. While it does appear to be a fact that hemorrhagic renal infarction may take place without significant thrombosis of renal veins, it is nevertheless true that in most cases, the venous thrombosis caused the infarction. No other interpretation is plausible in those instances in which renal infarction occurred after the thrombosis extended into the renal veins from the inferior vena cava. What remains unclear is (1) the reason for the relatively high incidence of these hemorrhagic infarctions in infancy and particularly in the neonatal period, (2) the reason for the total infarction without an organic vascular basis in some of the cases, and (3) the reason for the thrombosis of the renal vein in the presence usually of gastroenteritis. Bacteriologic and histologic studies of the thrombus and the wall of the vein in these instances are not illuminating.

#### *Renal Vein Thrombosis in Adults*

In the adult, thrombosis of the main renal vein produces, generally, not hemorrhagic infarction (plate 263C), but a clinical picture of

the nephrotic syndrome (Derow et al; Bell) (plate 264); hypertension was also present in Bell's case which followed nonlethal exposure to hydrogen cyanide. The nephrotic syndrome appears to be principally on the basis of the protracted loss of protein, especially albumin, in the urine as a consequence of abnormal glomerular permeability from the transmitted effects of increased venous pressure. In line with this is the suggestion that orthostatic albuminuria may be caused by pressure on the left renal vein as an effect of lordosis. Recently, it has been shown experimentally that increased pressure in the main renal vein results in an increased reabsorption of salt and water (Blake et al); these factors could, of course, enhance the edema of the nephrotic syndrome secondary to thrombosis of the renal veins.

With severe proteinuria, there ensues hypoproteinemia, reversal of albumin-globulin ratio, hypercholesterolemia, edema—a mechanism and sequence of events that is a common denominator of other forms of the clinical nephrotic syndrome. Kidneys in patients with the nephrotic syndrome secondary to thrombosis of the main renal vein exhibit little alteration in contrast to those of the newborn. The nephrotic kidneys are slightly to moderately enlarged and histologically show little more than moderate tubular atrophy and interstitial edema with fibrosis (plate 264). Again, the reason for this tremendous disparity in reaction to venous thrombosis in infants and adults must be the difference in collateral circulation available. In plate 263, for example, diffuse intrarenal thrombosis secondary to shock is illustrated in the kidney of an adult in which minimal histologic changes were present.

#### CORTICAL NECROSIS

Bilateral cortical necrosis (symmetrical cortical necrosis) was first described by Juhel-Rénoy in 1886; the patient was a 16 year old girl with scarlet fever. Up to 1941, 71 cases had been reported (Duff and More). In recent years, interest in this dramatic clinical and pathologic entity has been revived, particularly on the basis of the experiments of Trueta and his colleagues on renal hemodynamics.



### *Etiology*

Bilateral cortical necrosis occurs predominantly but not exclusively during pregnancy. It may follow poisoning by diethylene glycol, dioxane, dipropylene glycol, methyl and butyl carbitol, the administration of camphor intravenously, thyroid extract, cobra venom, and alcohol, and it may occur in association with burns, shock and with various infections such as diphtheria, scarlet fever, cholera, pneumonia, dysentery and therapeutic malaria. Unilateral cortical necrosis has followed thrombosis of the contralateral renal artery (plates 223, 226). Bilateral cortical necrosis is a different pathologic entity from the hemorrhagic infarction of the kidneys in infants with thrombosis of renal vessels.

### *Clinical Picture*

The clinical signs and symptoms are essentially the same in all cases regardless of the underlying background. Extreme oliguria or anuria, pain in the epigastrium radiating to the loins or along the course of the ureters, dependent or generalized edema in over a third of the cases and the terminal features of uremia comprise the clinical picture. The blood pressure shows no trend toward hypertension. Albumin, white blood cells, hyaline and granular casts are usually present in the urine. The urine prior to the onset of anuria is generally grossly bloody. Death occurs in from 2 to 32 days after the suppression of the urine. In some patients, anuria is followed by oliguria before death.

Inasmuch as most of the cases, approximately two-thirds, are associated with pregnancy, this feature merits some elaboration. Less than two-thirds of the patients are multipara. In about 85 per cent, the renal lesions occur prior to full term; in the remainder, the complication takes place near the time of delivery. In one instance the anuria occurred 13 days after delivery (Iungano). In about 25 per cent, the pregnancy is otherwise uneventful, in the remainder of cases, preeclampsia or eclampsia is present, and the membranous glomerular lesions of this toxemia may be found in conjunction with cortical necrosis (plate 103). In almost 40 per cent of cases, there is some evidence of renal dysfunction antedating

the cortical necrosis. Retroplacental hemorrhage is a frequently associated condition.

### *Pathology*

#### *Gross appearance*

The kidneys are moderately swollen and soft and the capsules are easily stripped from purple-red or red and yellow, mottled surfaces. Longitudinal sections reveal usually a spared, immediately subcapsular reddish brown strip of 1 to 2 mm., beneath which the remainder of the cortex is abruptly demarcated by a yellowish grey necrotic zone extending the length of the kidneys (plate 266A), including the cortical columns of Bertin. In some instances, the cortical involvement is incomplete and the cortical zone is made up of multiple grey infarcted wedges rimmed by deeply hyperemic margins. Usually the inner, or juxtamedullary half or third of the cortex is spared, but occasionally the entire cortex and rarely even the medulla (Scriven and Oertel) may be involved. The renal vessels are not grossly altered although in one of our cases, a thrombosis of the contralateral, markedly sclerotic main renal artery was found (plates 225, 226).

In addition to necrosis of the kidneys, infarct-like necrosis of the anterior lobe of the pituitary (Doniach and Walker; Sheldon and Hertig) and of the tuber cinereum may be present. Infarction of the anterior lobe of the pituitary gland attributed to shock, was noted also in one of our cases following an incompatible transfusion with resultant hemoglobinuric nephrosis (plate 129C).

#### *Histologic appearance*

As stated, the narrow subcapsular cortical zone is usually although not invariably intact, presumably because of collateral capsular circulation (plate 266A, B). This zone is bordered by hyperemic glomeruli and vessels as are the lower and lateral boundaries of the infarcted areas. The necrosis of the cortical components, that is, glomeruli, tubules, interstitium and vessels, is essentially similar to that of single renal infarcts. The extreme dilatation of glomerular capillaries (plate 266C) is a conspicuous feature which has been variously interpreted as reflecting vasoparalysis or a stage of

PLATE 268. RENAL CORTICAL "SHUNT" OF TRUETA: RADIOMICROGRAPHS OF KIDNEY OF RABBIT FOLLOWING IN VIVO INJECTION OF COLLOIDAL BISMUTH

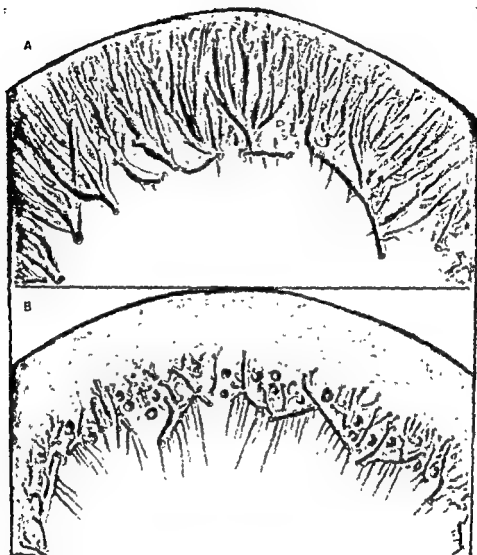


FIG. A. Right kidney of a rabbit showing the abundant normal distribution of radio opaque material within the diffusely patent cortical vessels and glomeruli.

FIG. B. Left kidney of the same rabbit in which the nerve plexus about the left renal artery was stimulated with faradic current. The result is an ischemic cortex with constriction of the peripheral segments of the interlobular arteries but with congestion of the juxtamedullary glomeruli and the vasa recta of the medulla. Trueta and his associates interpret this distribution of blood as indicative of a bypass of the cortical blood through the juxtamedullary glomeruli. Actually the cortical (i.e., the outer cortical) glomeruli in human cases of cortical necrosis as well as hemoglobinuric nephrosis are commonly intensely congested in contrast to the above phenomenon in rabbits (compare plate 268B). (These drawings are based on radiomicrographs from Trueta's *Studies of the Renal Circulation*, Springfield, C. C. Thomas, 1947, pp. 116-117.)

acute necrotizing glomerulonephritis (Dunn and Montgomery). Recent thrombi are generally present in the afferent arterioles, the interlobular arteries, and often in the arcuate arteries (plate 266C). These vessels, thus thrombosed, often show a fibrinoid necrosis of their walls. A noteworthy feature of this fibrinoid necrosis is that it may involve an "upper" or "outer" segment of an arcuate artery and spare the "lower" or "inner" segment as if the cortex had been sharply swathed by a necrotizing agent leaving the juxtamedullary portion abruptly intact (plate 266C). The hemodynamics of this selective pattern of necrosis of the wall of a vessel is not clear even if Trueta's debatable concept is invoked.

Interstitial, glomerular and tubular hemorrhage may be marked. Foci of polymorphonuclear leukocytes, often more or less karyorrhectic, are commonly present just as they are in simple renal infarcts. The medulla is hyperemic and is almost always spared, the medulla is usually intact in ordinary infarcts as well. As mentioned, the columns of Bertin containing cortical tissue may, of course, be involved.

#### *Associated lesions*

Bilateral cortical necrosis may be associated with other renal lesions produced, however, by different pathogenetic mechanisms. For example, the characteristic hydropic change of the tubular epithelium in diethylene glycol poisoning occurs with or without cortical necrosis (plate 120). Similarly, in pregnancy, cortical necrosis may be combined with acute membranous glomerulonephritis. Such a combination in either instance is not to be interpreted as indicating the same pathogenesis for each of the component lesions.

#### *Pathogenesis*

Experimentally, bilateral cortical necrosis of the kidneys has been produced with pitressin (Byrom), adrenalin (Penner and Bernheim), staphylococcal toxin (De Navasquez), and daily intravenous administration of lithium carmine in rabbits for two to six days according to Gurnez Reyna. There is a current trend to attribute the cortical necrosis to shock but the production of the lesion in humans by various

chemical agents indicates other mechanisms may play a part. Duff and More suggest a vascular hypersensitivity. Dunn and Montgomery postulate any one of three mechanisms are involved in cortical necrosis: (1) acute necrotizing glomerulonephritis, (2) ischemia and (3) veno-stasis secondary to renal vein thrombosis. Embolization, including fat embolization and primary thrombosis of damaged renal arteries, has had its advocates. Theories of renal vasomotor disturbances, despite their admittedly vague definition, have had most appeal (Scraper and Oertel; Ash).

Whatever the basic stimulus and its mode of application is, however, the concept of Trueta and his associates of this particular hemodynamic derangement seems most apt. They have vividly demonstrated in rabbits that crushing the muscles of an extremity, stimulating the sciatic nerve, or injecting pitressin is followed by ischemia of most of the cortex and hyperemia of the juxtamedullary glomeruli and medulla. The result is symmetrical cortical necrosis of the kidneys. In other words, with appropriate neural stimulation there is a diversion of blood from the outer to the inner cortical zone, leaving the outer zone relatively bloodless.

Although the vagaries of the rabbit as an experimental animal are well known, the Trueta concept for the explanation of cortical necrosis seems the most fitting to date. However, the intense hyperemia of the outer cortical glomeruli in human cases constitutes a basic discrepancy in the application of the results in rabbits to humans.

#### *Prognosis*

There is no positive evidence that patients may survive bilateral massive cortical necrosis. A number of instances of such recovery are recorded but proof is lacking that the clinical picture of cortical necrosis was not simulated by some other serious renal lesion such as hemoglobinuric nephrosis or incomplete cortical ischemia falling short of necrosis. Certainly one does not see at autopsies kidneys which appear to represent a healed stage of bilateral cortical necrosis.



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Although the vagaries of the rabbit as an experimental animal are well known, the Trueta concept for the explanation of cortical necrosis seems the most fitting to date. However, the intense hyperemia of the outer cortical glomeruli in human cases constitutes a basic discrepancy in the application of the results in rabbits to humans.

#### *Prognosis*

There is no positive evidence that patients may survive bilateral massive cortical necrosis. A number of instances of such recovery are recorded but proof is lacking that the clinical picture of cortical necrosis was not simulated by some other serious renal lesion such as hemoglobinuric nephrosis or incomplete cortical ischemia falling short of necrosis. Certainly one does not see at autopsies kidneys which appear to represent a healed stage of bilateral cortical necrosis.



FIG A Fat embolism as evidenced by clear spaces in glomeruli and peritubular capillaries. The embolism followed extensive fractures of bones. No glomerular reaction or tubular atrophy is present. Renal function is rarely compromised by fat emboli. (A F I P Acc 105694)

FIG B Sudan III stain of section in figure A, demonstrating the black lipid masses in glomerular and peritubular capillaries.



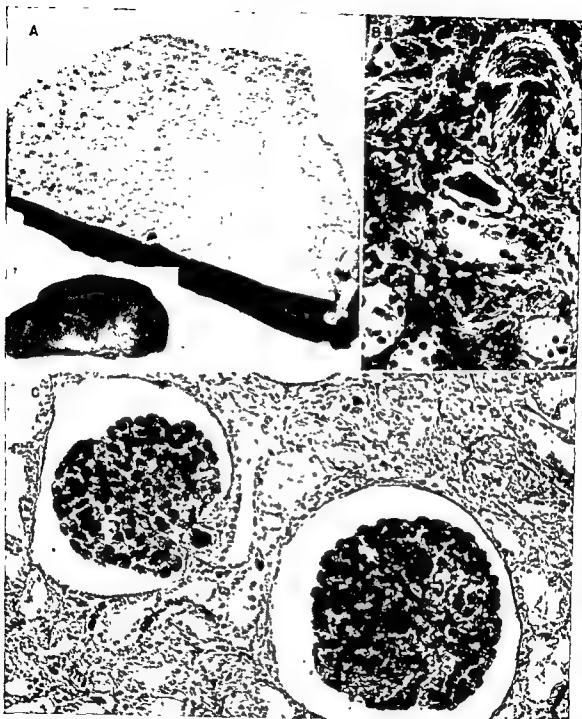


FIG. A Sickling in kidney is characterized grossly by large congested glomeruli

FIG. B Sickled cells in interlobular veins of kidney (formalin fixation) Sickling is not demonstrable in paraffin sections of Zenker fixed tissue

FIG. C Sickled cells in glomeruli with extreme congestion due to compacted, sickled red blood cells Sickling of erythrocytes within the kidney may be responsible for severe hematuria

## FAT EMBOLI TO KIDNEY

Very little has been added to our information on fat embolization to the kidney since the time of Vance's report in 1931. Fat embolism follows trauma to fat whether the fat be in bone marrow or in soft tissue more superficially. Fat embolism results from fractures of bones, jarring of the skeleton, orthopedic operations, trauma to viscera and to subcutaneous and intermuscular fat, the intravenous injection or intraurethral instillation of various oils, volatile anesthetics, burns, sickle cell anemia and various poisons. The mode of death caused by fat embolism is (1) cerebral, or (2) pulmonary, depending on the extent of the capillary bed occluded and the location of vessels in the brain. Microinfarcts with ring hemorrhages occur in the brain but not in the lungs. Death may follow embolization in from a few seconds to several days; deaths delayed 25 days have been recorded (Warren).

The kidneys are rarely spared some degree of fat embolization in these cases. There is a difference of opinion as to whether or not extensive lipid embolization causes renal dysfunction. The bulk of opinion is that the emboli do not produce significant renal embarrassment, contrary opinion has been recorded (Buse, Paul and Windholz). Possibly the dysfunction may be dependent on antecedent renal disease or the shock in such instances.

The histologic picture of renal fat embolism, as observed in paraffin sections is characterized by focally dilated, bloodless, clear spaces within the glomerular capillaries. The endothelial cells are flattened and the basement membrane stretched. These spaces are occupied by fat as demonstrated with Sudan stains or osmic acid (plate 269). Lipid is present also in some of the peritubular capillaries. The remarkable feature of the lesion is the total lack of reaction about the emboli. Lipiduria occurs commonly in these

cases and may furnish the lead to the clinical diagnosis.

## ANEURYSM OF RENAL ARTERY

Aneurysms of the renal artery occur rarely but may have grave consequences and therefore deserve a note. As in other locations, the aneurysms are divided into (1) true and (2) false. The true aneurysm is caused by trauma to an intact artery or one weakened by arteriosclerosis, mycotic arteritis (plate 259A, B), periarteritis nodosa (plate 228B), syphilis, and congenital defects. The false aneurysm is almost always the result of trauma with rupture of the artery and occlusion of the defect by blood clot. The false aneurysm, which differs from the true aneurysm in that its wall is not made up of the three arterial coats but merely of organized clot, comprises about 15 per cent of the lesions.

There are usually no symptoms of aneurysm of the renal artery until rupture occurs. Occasionally abnormal pulsations, bruits, and murmurs are detected, and, in addition, there may be intermittent pain, recurrent hematuria, and even a palpable mass. Hematuria may result from renal infarction or from perforation of the renal pelvis. Radiologists may suggest the diagnosis on the basis of calcification ("ring shadow") of the wall of the aneurysm. The calcified ring is incomplete at the point of origin of the aneurysm. Such a density would have to be distinguished from renal calculi, cholelithiasis, or calcified lymph nodes. Undiagnosed aneurysms have been ruptured inadvertently during operations in the region of the kidney. Hypertension was present in 11 of the 56 cases of aneurysm of the renal artery reported since 1927, in 3 of these 11 patients, the hypertension was restored to a normal level after operation (Berneke and Pollack).

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# 14. Tumors of the Kidney

## Introduction

THERE are many varieties of renal tumors, but it is fair to state that, except for the parenchymatous carcinomas, the pelvic papillomas and carcinomas, and the Wilms' tumors, the others are either oddities, or relatively insignificant from a clinical point of view. Grossly discernible benign tumors of the kidney are found in about 5 per cent of kidneys. Renal cancers constitute approximately 13 per cent of all cancers, the incidence is higher in males than in females (Macdonald).

## Clinical features

The cardinal signs and symptoms of a renal tumor are, in order of frequency: (1) painless hematuria, (2) local pain unrelated to hematuria, and (3) a palpable mass, the reversal of this order of frequency holds in the case of Wilms' tumors. In addition, compression, elongation, dilatation, distortion or filling defect of renal calyces or pelvis as revealed by intravenous and especially by retrograde pyelography, particularly if associated with calcium flecks in the mass, constitute confirmatory evidence. All of this evidence may be produced by benign or malignant renal tumors, or by retroperitoneal, extrarenal tumors which have encroached on the kidney. On the other hand, benign or malignant tumors of the kidney may remain clinically silent, and in the case of the latter, may nevertheless give rise to extensive metastases. Renal tumors may be simulated by mesenteric cysts, neoplasms of the sigmoid and descending colon, pancreatic masses, splenomegaly, Reidel's lobe of the liver, enlargement of regional lymph nodes, and cysts or tumors of the female internal genital organs. In any case of unexplained hematuria, the possibility of renal tumor must be ruled out. Other general signs and symptoms that may be present include fever, chills, anemia, weight loss, anorexia, leukocytosis, and varicocele secondary to

involvement of the spermatic or ovarian vein, particularly on the left side where they enter the renal vein (Bonniecarrere). Malignant tumors of the kidney are about twice as common in males as in females, and, exclusive of the Wilms' tumors, are most common in the sixth and seventh decades. They occur with equal frequency in either kidney. Bilateral parenchymal renal malignant neoplasms are rare. Occasionally, metastases are taken for bilaterality.

Renal tumors may occasionally be associated with the development of hypertension and with its regression after nephrectomy. The problem of causal relation is the same as in other types of unilateral renal disease and is equally unsettled. In the case of the renal tumors, it is to be remembered that many of them occur at an age when hypertension is common.

Although benign and malignant tumors occur in anomalous kidneys, there is no statistically significant evidence of their predisposition to neoplastic growth.

## Diagnosis from exfoliated cells

Recently, the diagnosis of renal neoplasms from examination of smears and blocks of the urinary sediment for neoplastic cells has been advocated (Foot and Papanicolaou). Plate 293B, C, and D are examples of such sediments. However, this procedure requires the keenest kind of evaluation and is fraught with hazards. One such pitfall is the mistaking of regenerating or otherwise altered parenchymal tubular cells for cancer cells (plate 309B). Another error may result from pushing the cells of a bladder cancer up into the ureter by means of a catheter with the consequent diagnosis of renal cancer and subsequent nephrectomy (Staff of St Vincent's). A frank evaluation of the problem is presented by Bunge and Krausbaa who report two cases in which normal kidneys were found



FIG A *Tubular cortical adenomas* located just beneath the capsule are indicated as small grey nodules (arrow). These nodules are grossly similar to small adrenal rests, lipomas, fibromas, leiomyomas or angiolipomas.

FIG C *Minute tubular cystadenoma*, away from the capsule and deep in the cortex, clearly suggesting origin from epithelium of distal tubules in this instance. Microcysts, as shown here, are also frequently present.

FIG B *Tubular papillary cystadenoma*, made up of papillary projections, as if the tubular epithelium had undergone epithelial hyperplasia. The transition from the normal tubules at the periphery is illustrated.

FIG D *Papillary tubular adenoma* with interstitial deposits of lipid histiocytes, common in these tumors and their malignant counterpart.

PLATE 272. BENIGN NEOPLASMS: TUBULAR ADENOMAS

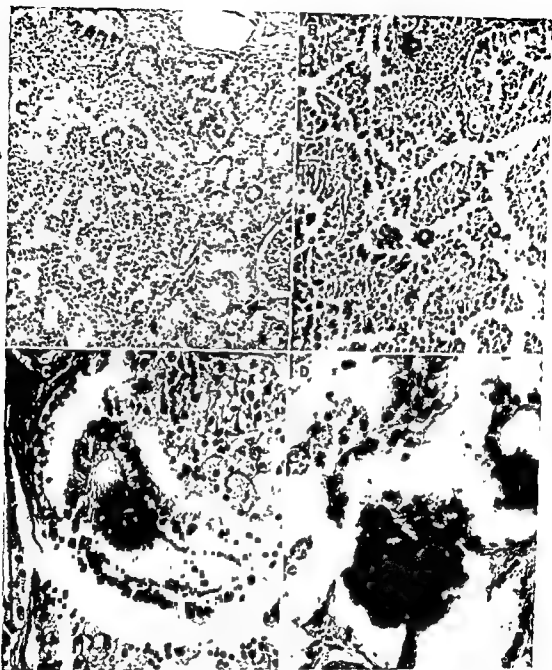


FIG A Nonencapsulated tubular papillary cystadenoma, showing origin from tubular epithelium in multiple foci

FIG C Calcified body within serum of venule of frond of a tubular adenoma.

FIG B Psammomatous bodies in the fronds of a papillary adenoma

FIG D Calcific body resulting from encrusting of epithelial cells of a papillary adenoma



FIG A *Partially trabeculated cyst of upper pole of kidney with small papillary adenoma illustrated in figures B and C*



PLATE 274. BENIGN NEOPLASMS: CORTICAL (TUBULAR) ADENOMA



FIGS A AND B Circumscribed solid tubular adenoma of kidney and dilated pelvis (B) resulting from pressure by the tumor (*J Urol* 56 719-721, 1948)

FIG C Circumscribed cortical (tubular) adenoma of kidney with central cyst

FIG D Cortical (tubular) adenoma (1.5 cm in diameter) with compression of adjacent parenchyma into a pseudocapsule Unlike those in figures A, B, and C, this one would most probably have eventually metastasized

PLATE 275. BENIGN NEOPLASMS: CORTICAL (TUBULAR) ADENOMAS



FIG A Cortical (tubular) adenoma sharply delimited from adjacent renal parenchyma

FIG B Papillary cortical (tubular) adenoma

FIG C Cortical (tubular) adenoma of kidney The individual cells resemble those of distal convoluted tubules

FIG D Cortical (tubular) adenoma of kidney with ossification of adjacent lipoma of cortex

despite a report of abnormal cytology in the urinary sediment.

### Experimental renal carcinogenesis

Experimentally, cortical adenomas and low-grade adenocarcinomas have been produced bilaterally in the kidneys of male hamsters in which pellets of diethylstilbesterol were implanted subcutaneously. No tumors were induced in females, nor in those males in which the pellets contained cholesterol in addition to diethylstilbesterol (Kirkman and Bacon).

### Classification

Again, as with most classifications in pathology, the overlapping of origins, cellular patterns, and the differences of opinion with regard to their nature and significance, leave any categorization of renal tumors open to some criticism. The outline used here has no real advantage over others, but it does include the division of hamartomas which serves a purpose if it is only to give opportunity to define and illustrate a much confused term. The other major source of difficulty in attaching a name to renal neoplasms, especially the carcinomas, is the diversity and prognostic meaning of their various cellular types.

## CLASSIFICATION OF RENAL TUMORS

### Tumors of the Renal Parenchyma

Benign  
 Cortical (tubular) adenoma  
   Solid  
   Cystic  
 Fibroma  
 Lipoma  
 Myxoma  
 Angioma  
 Lymphangioma  
 Hemangiopericytoma  
 Leiomyoma

FIG A Adrenal gland growing both within the renal parenchyma and extracapsularly. Histologic section is shown in figure D

Mixed tumor with combination of above elements—angiomyolipoma, myxolipoma, etc  
 Dysontogenetic rests  
 Adrenal cortical rests  
 Chondral and osseous rests  
 Dermoid cysts  
 Endometrioma  
 Malignant  
 Adenocarcinoma (tubular) (Grawitz tumor; hypernephroma)  
 Wilms' tumor  
 Fibrosarcoma  
 Liposarcoma  
 Leiomyosarcoma  
 Angiosarcoma and other compounded sarcomas  
 Metastatic tumors

### Tumors of the Renal Pelvis

Papilloma  
 Papillary transitional cell (epidermoid) or squamous cell carcinoma  
 Nonpapillary transitional cell (epidermoid) or squamous cell carcinoma  
 Mucous adenocarcinoma

### Tumors of the Renal Capsule

Fibroma  
 Lipoma  
 Angioma  
 Leiomyoma  
 Myxoma  
 Tumors with combinations of the above elements and their malignant counterpart

### Tumors of the Paranephric Tissue

Tumors of type found in renal capsule  
 Extra-osseous osteogenic sarcoma

## TUMORS OF THE RENAL PARENCHYMA

### Cortical (Tubular) Adenomas

Cortical (tubular) adenomas are a common incidental finding at postmortem examinations of people past middle age, occurring in about 4 per cent of kidneys examined at autopsy. They are usually pinhead sized to about 3 cm. in diameter (plate 271A), but may become huge

FIG B Adrenal cortical rest (arrow) is grossly similar to a cortical lipoma or adenoma

FIG C Adrenal cortical rest. The adrenal cells are in the upper two-thirds of the photomicrograph, renal tubules are in the lower portion.



(Legends on facing page)

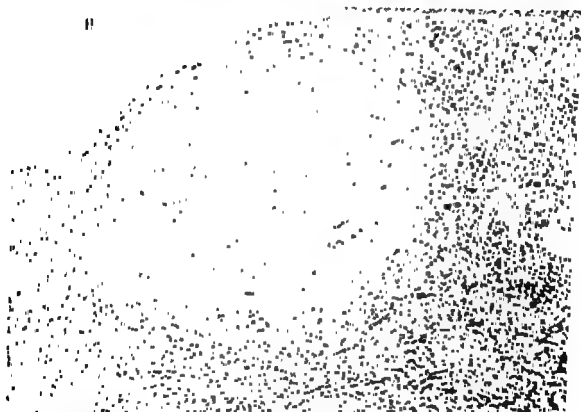


FIG A *Medullary fibromas* (arrows)

FIG B. *Medullary fibroma* with a few isolated residual tubules that are commonly found in these lesions

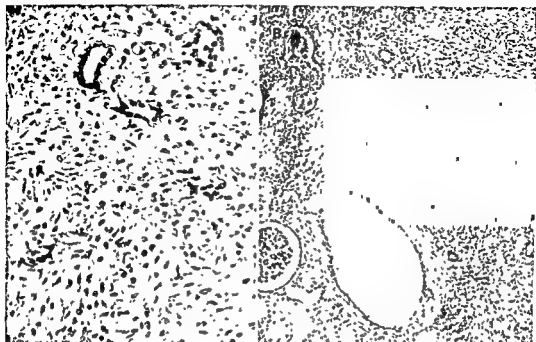


FIG A *Medullary fibroma* with tubular inclusions and the characteristically loose stroma which is often partially hyalinized

FIG B *Cortical fibroma* of identical pattern as the medullary fibromas. These cortical fibromas are much less common

FIG C *Mild lipomatosis* secondary to parenchymal atrophy. In extreme forms, the fat may occupy the whole original volume of the kidney and the perirenal fat may also be markedly increased

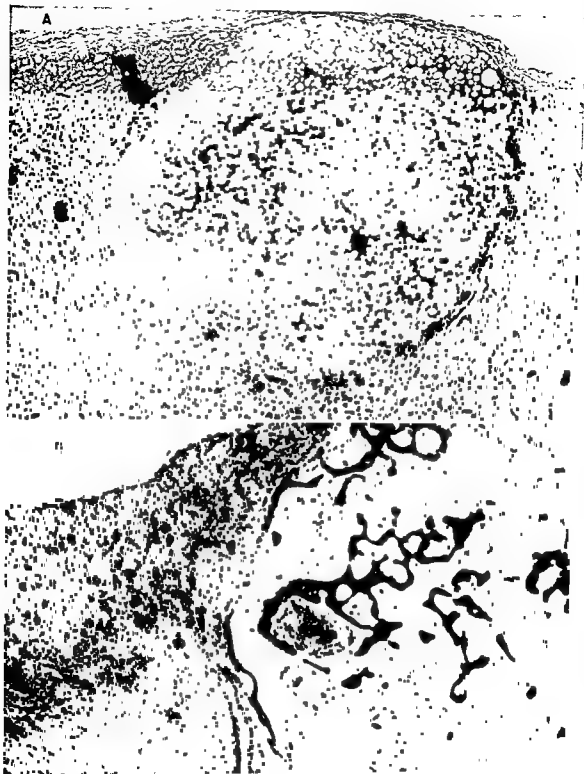


FIG A *Cortical lipoma of kidney*

FIG B *Cortical osteolipoma of kidney* The bone is a result of metaplasia rather than dysontogenesis



FIG A. Hemangioma of kidney (arrows) with blood clot in adjacent calyx and pelvis

FIG B Hemangioma of kidney, this photomicrograph is taken from lesion in figure A. Such lesions may cause massive or fatal hematuria

FIG C Varix of the kidney. This lesion is commonly mistaken for hemangioma or lymphangioma of the kidney



and develop into a mass about the size of a grapefruit (plate 274A, B, C) They may be cystic or solid The cystic ones often develop in cortical scars and are somewhat reminiscent of the papillary hydrocystadenomas of sweat gland origin that seem to follow occlusion of the duct of the sweat gland in some cases. Bell is confident that the renal papillary cystadenomas do not ever become metastasizing carcinomas; others disagree (Cristol et al, Cabot and Middleton, Leary) Papillary cystadenocarcinomas do occur

The solid ones are yellow, soft, spherical nodules located often immediately subcapsular, but also in other portions of the cortex The smaller tumors may be grossly indistinguishable from adrenal cortical rests, lipomas, angiolipomas, leiomyomas and the cortical fibromas. Cortical (tubular) adenomas rarely cause symptoms, although the larger ones (plate 274A, B, C), of which 50 were in the literature up to 1930 (Cristol et al), may result in hematuria, hydronephrosis, pain, and a palpable mass. The large clinically evident adenomas occur equally in both sexes (Cristol et al), although the small incidental ones are about three times as common in men (Cristol et al) Bell states that he arbitrarily classifies all "solid adenomas" larger than 3 cm in diameter as carcinoma Obviously there are many exceptions to this rule

### *Histologic appearance*

The early, or better, smaller tubular adenomas—particularly those that consist of small cysts with proliferation of only a small portion of the lining—clearly indicate their origin from tubular epithelium rather than adrenal cortical rests It is this stage of the tubular adenoma which has led to the almost general replacement of the old concept that the Grawitz tumor is derived from adrenal rests within the kidney (hence, the old term "hypernephroma") by the concept of their derivation from renal tubular epithelium or renal tubular adenomas (Cristol et al) In the very small cysts, the residual tubular epithelium, not yet converted to adenoma, appears indistinguishable from that of distal convoluted tubules, and occasionally from the proximal convoluted tubules (plate 271B, C).

Cholesterol and birefringent crystalline cholesterol esters, and occasionally glycogen may be present in the cells; often lipid histiocytes are prominent in the interstitium. The neoplastic cells are usually remarkably uniform in size and shape, and mitotic figures or evidence of anaplasia is most uncommon. In some of the larger tumors, the vascularity is conspicuous, often in the form of dilated thin-walled sinuses.

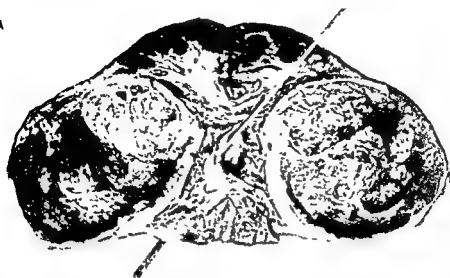
In the cystic tumors, a nidus of papillary proliferation begins often at one segment of the epithelial lining and may or may not progress to obliterate the cavity. The papillary fronds may become markedly edematous (plate 273)

### *Adrenal rests*

Small, single or occasionally multiple, tawny soft nodules of adrenal cortical tissue, averaging 3-5 mm. in diameter, are found in the subcapsular regions of the kidney (plate 276B), usually near the superior pole, in about 1 per cent of routine autopsy material. Obviously, the disparity in reported incidence of such rests reflects the care of the observers in their search for these small bodies Histologically the nodules are composed only of adrenal cortical tissue (plate 276C), of course, and all three zones may be present although the reticularis is noted less often than the glomerulosa and fasciculata. These rests have no apparent clinical significance. There is no longer any but the most tenuous evidence to support the concept that the rests give rise to "hypernephromas" (clear cell renal adenocarcinoma). The association of the adrenal rests with papillary cysts or with renal carcinoma in another part of the kidney can hardly be regarded as indicative of a histogenetic relationship, as some believe The coincidental finding of renal clear cell adenocarcinoma and adrenal rests in the same kidney is therefore not unexpected on the basis merely of chance occurrence.

In addition to rests of adrenal cortical tissue within the renal parenchyma, small histologic foci or nodules and plaques of bone and cartilage are occasionally found, particularly in the medulla The bone generally appears to be metaplastic rather than dysplastic rests The chondral foci are usually true rests composed of hyaline cartilage and are said never to be found

A



B



FIG A *Endometriosis of kidney* The hemorrhagic cyst occupies more than half of the kidney (Courtesy of Dr V L Marshall, *J Urol* 50 652-656, 1943)

FIG B *Endometriosis of kidney* This photomicrograph was taken from a section of lesion illustrated above, and shows easily recognizable endometrial glands and stroma Only two such cases have been reported

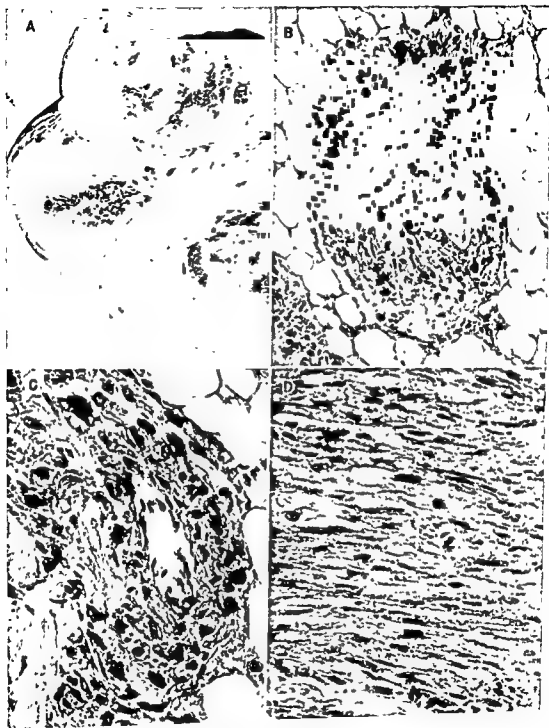


FIG A *Angiomyolipoma of kidney* Soft, unencapsulated, yellowish-red mass projecting from the cortex.

FIG C *Angiomyolipoma of kidney* The tumor cells are clearly arising in the medulla of the vessel

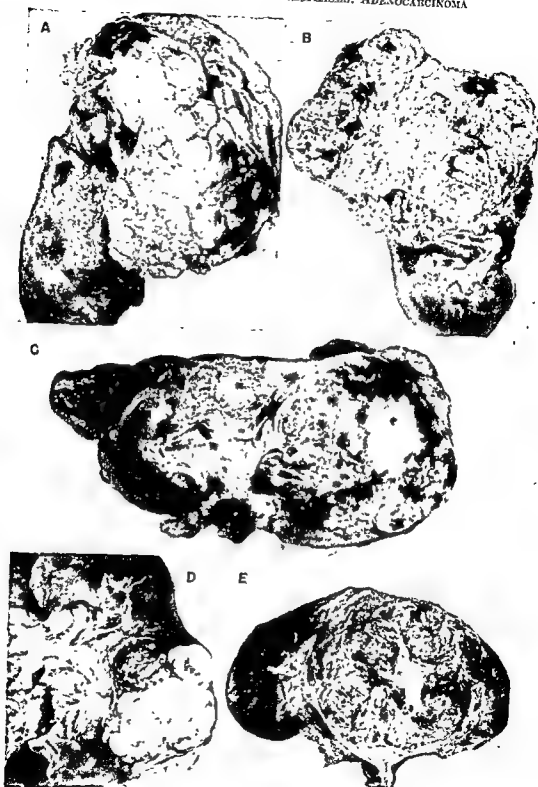
FIG B *Angiomyolipoma of kidney* with tumor cells radiating from the medulla of the vessels into the fat

FIG D. *Angiomyolipoma of kidney* showing purely myomatous variation in one portion



FIGS. A AND B. *Angiomyolipoma of kidney showing the usual components of partially hyalinized vessels, fat and peribellally arranged muscle cells*

PLATE 284. MALIGNANT NEOPLASMS: ADENOCARCINOMA



FIGS A THROUGH E represent examples of *adenocarcinomas* (tubular) of the kidney, formerly called hypernephromas or Grawitz tumors

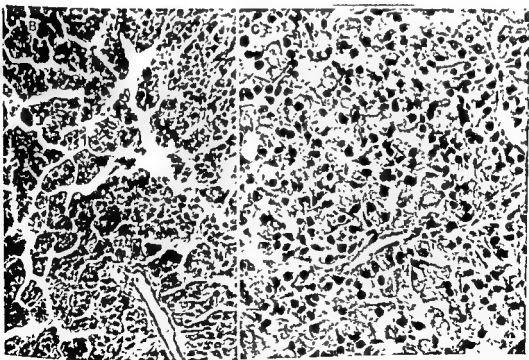


FIG A Hemorrhagic papillary tubular adenocarcinoma of upper pole of kidney with nodule of tumor in vein

FIGS B AND C Papillary tubular adenocarcinoma from tumor illustrated in figure A. The cells have a granular cytoplasm.

in kidneys without other *congenital deformities* (Killingsworth). However, although cartilaginous rests are commonly observed in association with cystic kidneys (plate 40B), they may be found also in neoplasms (plate 299B, C) and even in the absence of congenital anomalies of the kidney (plate 300A).

### *Lipomas*

Lipomas are a fairly common tumor not only of the parenchyma but of the renal capsule and paranephric tissue. The parenchymal lipomas are usually small spherical soft nodules of the order of 3 to 5 mm in diameter, located, as a rule, in the subcapsular portion of the cortex (plate 279A). Infrequently the lipomas from any of these sites of origin, but particularly from the paranephric fat, may become large and cause symptoms of any renal tumefaction (Robertson and Hand). A lipoma originating from the adipose tissue near the hilum may invaginate the renal pelvis and simulate a tumor arising from the pelvis.

The lipomas are frequently compounded with hemangiomatous and myogenous components (plates 282B, C and 283A, B) to form tumors called angiomyolipomas or, more generally, hamartomas. The affinity for hemangiomatous expansion in adipose tissue is well known in other locations, especially in the extremities. The muscle cells in these tumors have a peritheliomatous pattern and appear to arise from the media of the blood vessels (plate 282C). The proportion of fat, muscle and blood vessels is highly variable (plates 282, 283). Metastases from these lesions are an extremely rare occurrence. Nevertheless, neoplasms that histologically merit the designation of liposarcoma occasionally occur (McCartney and Wynne) and instances of metaplastic ossification, of chondrification, of inclusions of striated muscle and even osteosarcoma have been described within *pararenal lipomas* (plate 279B), as in lipomas elsewhere (Binkley and Stewart).

The large pararenal lipomas cause symptoms in relation to the degree of compression of adjacent viscera, blood vessels and ureters (Gordon-Taylor). These tumors occur predominantly in males. The operative mortality on

these large tumors is high (Pfeiffer and Gaudin) and the tendency for recurrence with increasing anaplasia is considerable. It is of interest that the pararenal lipomas do not diminish in size with cachexia of the patient (Pfeiffer and Gaudin).

### *Liposarcomas*

Up to 1949, only 13 cases of liposarcomas of the renal parenchyma had been reported, according to Newman and Reed. Of these, 7 were associated with tuberosus sclerosis. Most of the tumors are large, and only histologically malignant; *metastasis from these neoplasms has not been reported* (Bell). The histologic picture is variegated (plate 317B, C). Portions resemble a simple lipoma composed of adult fat cells, other parts contain embryonic, finely vacuolated fat cells, and still others take on the appearance of edematous, fibromatous or myxomatous tissue with abortive or typical Touton giant cells, and a basophilic mucoid matrix. Isolated fibroblastic appearing cells have large, hyperchromatic irregular nuclei of sarcomas. Because the sarcomatous portions may be found surrounded by simple adult fat cells, the impression has been gained that liposarcomas may represent a malignant degeneration of a lipoma. If this is in fact what occurs, then the phenomenon constitutes additional evidence for an important oncologic principle, namely, that a benign mesenchymal tumor may undergo sarcomatous transformation, in contradistinction to its having been a sarcoma from its initial stages.

### *Lipomatosis*

True lipomas are to be distinguished from the progressive pelvic, peripelvic, and pararenal replacement accumulation of fat, or lipomatosis, in cases that show parenchymal renal atrophy (plate 278C). The over-all dimensions of the kidneys in these cases may be considerably enlarged by the pelvic and pericalyceal fat. In one of Bell's cases, the kidney weighed over a thousand grams. Calculi and pyelonephritis, or simple senile arteriosclerotic atrophy, are commonly associated with renal lipomatosis. Renal lipomatosis may also be found in obese patients

PLATE 286. MALIGNANT NEOPLASMS: TUBULAR ADENOCARCINOMA

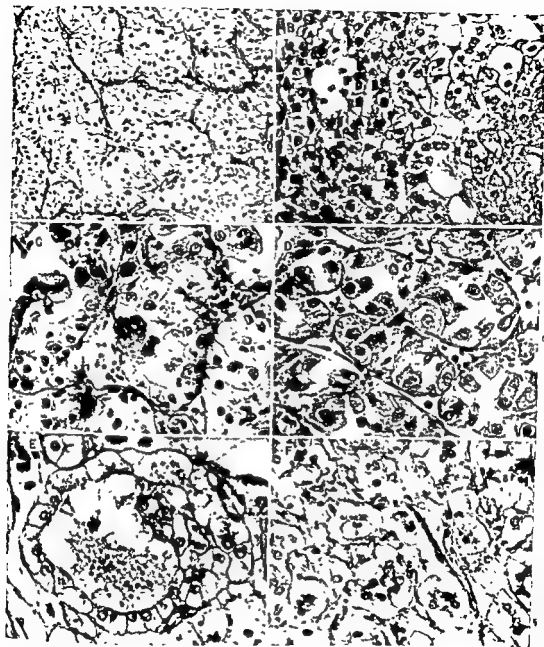


FIG A Clear cell tubular adenocarcinoma

FIG C Tubular adenocarcinoma with clear cells showing various degrees of granularity

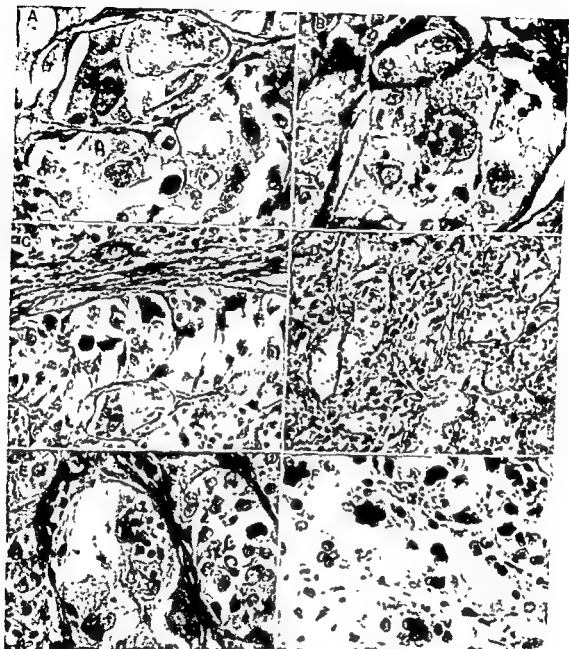
FIG B Tubular adenocarcinoma with granular and clear cells

FIG D Tubular adenocarcinoma composed of granular cells

FIGS E AND F Tubular (clear cell) carcinoma in which hemosiderin granules are noted within the cytoplasm, very much as in functioning tubules



PLATE 287. MALIGNANT NEOPLASMS: TUBULAR ADENOCARCINOMA (HISTOLOGIC VARIANTS)



FIGS A AND B *Tubular adenocarcinoma with huge, irregularly shaped nuclei and bizarre mitotic figures rather than the more usual uniform nuclei*

FIG C *Tubular adenocarcinoma with marked pleomorphism*

FIG E *Polymorphonuclear leukocytes are within the cytoplasm of a clear cell of a tubular adenocarcinoma as if they were phagocytosed by the cancer cell*

FIG D *Tubular adenocarcinoma with degrees of anaplasia varying in different fields*

FIG F *Syncytium of nuclei in a tubular adenocarcinoma simulating the syncytium that occurs normally in the proximal tubules in later decades*



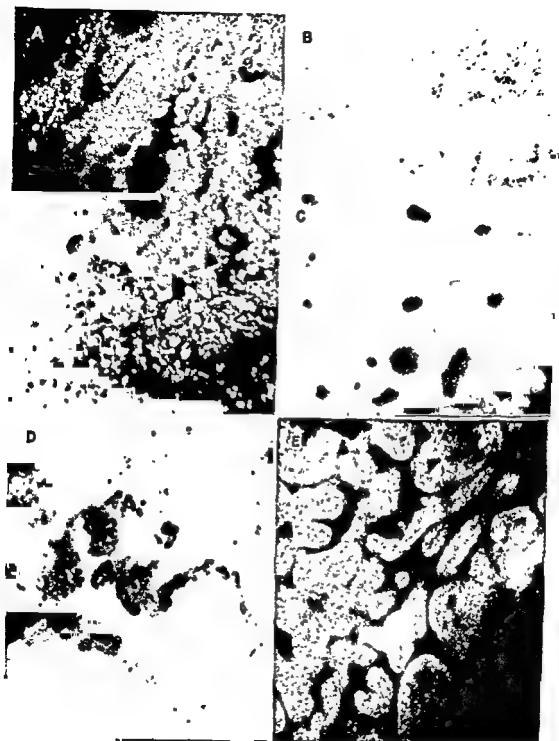
FIG A Papillary cystadenocarcinomatous variant of renal adenocarcinoma

FIG C Focal calcification in renal adenocarcinoma, occasionally visible in roentgenograms

FIG B Glycogenic and lipid vacuolization in renal adenocarcinoma

FIG D Hemosiderin in renal adenocarcinoma following spontaneous hemorrhages

PLATE 289. MALIGNANT NEOPLASMS: ADENOCARCINOMA



FIGS A THROUGH D represent the fluorescence attributable to vitamin A and shown here in renal adenocarcinoma. FIGURE E shows the fluorescence in a cortical adenoma of the adrenal for purposes of comparison (Courtesy of Dr Hans Popper, Arch Path. 52: 258-271, 1941)

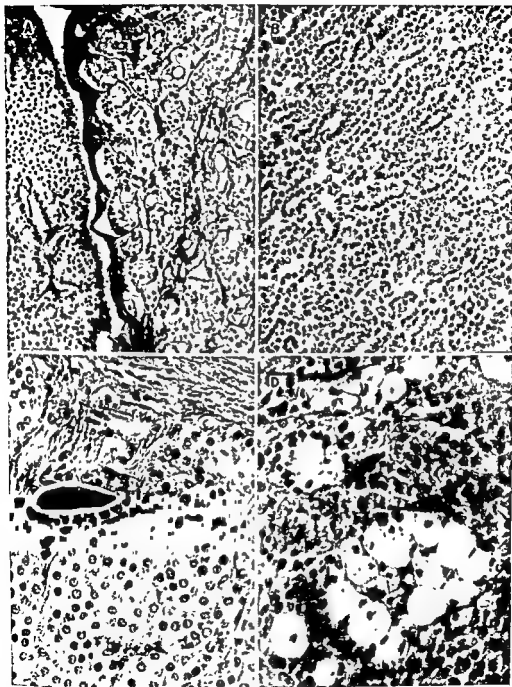


FIG A Variation in pattern in adjacent fields in renal adenocarcinoma

FIG B Well differentiated adenocarcinoma simulating distal tubules

FIG C Renal adenocarcinoma with solid nests of uniform cells

FIG D Renal adenocarcinoma with interstitial foam cells.

### *Fibromas*

Fibromas are not uncommonly found as greyish-white, spherical, single nodules, usually 3 to 5 mm. in diameter. As a rule, they are located in the medulla (plate 277A, B), and much less frequently in the cortex or capsule. They have clinical significance only rarely when they reach large size. The fibroma described by Gordon-Taylor weighed 22 pounds.

Histologically small fibromas are characterized by the inclusion of isolated renal tubules (plate 278A). Even the massive tumor just referred to had such inclusions and led to the diagnosis of adenofibroma. This tumor was intrarenal in location. The tubules are absent, of course, in the capsular and paranephric fibromas. The impression is gained that the tubules do not represent part of the neoplastic process but rather are simply incidental inclusions. The term "myxofibroma" is often used gratuitously for fibromas that have become edematous.

### *Hemangiomas*

Hemangiomas of the kidney are relatively rare benign tumors which occur at any age, are usually single, and are situated in the medulla or pelvis, rarely in the cortex. The tumors vary from 1 to 2 mm. to several centimeters in diameter, are spongy and dark red (plate 280A). Microscopically, they are found to be composed of thin-walled sinuses that often simulate lymphatic vessels, or sometimes, tubules (280B). The presence of blood in the lumens is diagnostically helpful, but, of course, blood may be found within lymphatic vessels or tubules. Even the small hemangiomas may be responsible for sudden massive hematuria. The hematuria may be irregularly intermittent, and associated with pain in the groin or flank. The diagnosis can rarely be made preoperatively because of the small size of the lesions, and commonly the cause of the lesion is labeled "essential hematuria." The lesions may be difficult to demonstrate even in the actual specimen (Dorman and Fowler).

### *Endometrioma*

According to Marshall, this is the only case of endometrioma of the kidney to have been re-

corded.\* The tumor in this instance was not on the surface of the kidney but definitely intrarenal (plate 281A). We had the opportunity to examine this remarkable specimen grossly. The tumor occupied the central portion of the 800 Gm. kidney, between its poles, and measured 10 x 13 cm. It was an irregularly multiloculated cystic mass, containing about 500 cc. of blood and had solid, fleshy portions. The patient was a 40 year old Greek woman who had noted a tender mass in the left flank and had hematuria on one occasion. The intravenous and retrograde pyelograms revealed marked calyceal deformity. The function of this kidney was reduced. There is little to be gained from our contributing to the controversy of the theories of dysontogenesis of an endometrial tumor in the kidney. The histologic features are definitely endometrial (plate 281B).

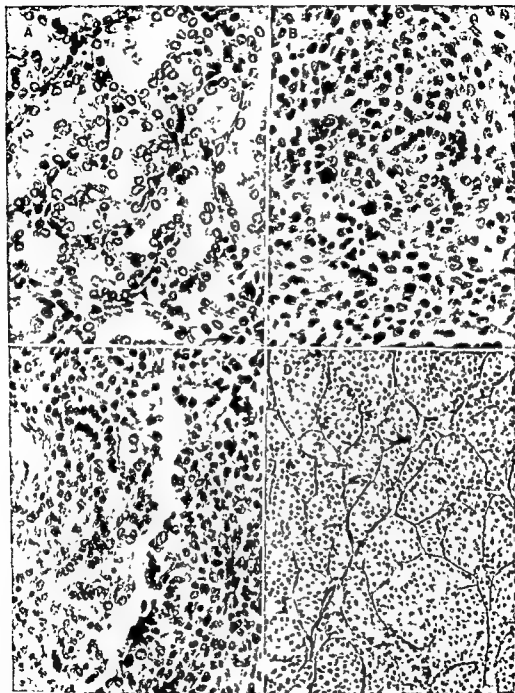
### *Leiomyomas*

Small 3-5 mm. leiomyomas are about as common as, and appear grossly similar to, the small fibromas, adenomas and lipomas. They are generally capsular or subcapsular. Occasionally, large parenchymal tumors are observed which seem to be composed entirely of fascicles of smooth muscle; others on careful search, are found to be predominantly leiomyomatous, but with foci of other elements, including clear cell carcinoma or areas suggesting renal blastema or Wilms' tumor. The large leiomyomas often have features that warrant the histologic diagnosis of leiomyosarcoma and occasionally these metastasize (Gordon, Kimmelstiel and Cabell; Cooke).

### *Tuberous Sclerosis*

Tuberous sclerosis is a familial disease of children and young adults characterized by progressive mental deterioration, epilepsy, sebaceous adenomas of the face and placoma of the retinae. Nodules of glial scars (tuberous sclerosis) are found in the cerebral cortex and, in over half the cases, there are associated hamartomas of various sorts in the kidneys. These renal tumors are usually multiple, of small size

\* A second case of renal endometriosis has been reported recently. *J. Urol.* 64: 565, 1950.



FIGS A THROUGH D represent variants of the well differentiated adenocarcinoma of relatively good prognosis. The basis for evaluating the malignancy of this type of neoplasm is often arbitrary and dependent on its size.



FIG A Caternomatous sinusoids in renal adenocarcinoma, thin walled and gaping for the reception of neoplastic cells

FIG C Metastases to venules of kidney from renal adenocarcinoma

FIG B Metastases to intrarenal lymphatic vessels from renal adenocarcinoma. Such widespread lymphatic involvement has offered clues to the anatomy of renal lymphatics

FIG D Isolated cells from adenocarcinoma (clear cell) in renal vein, possibly artefactually included in view of their lack of cohesion.

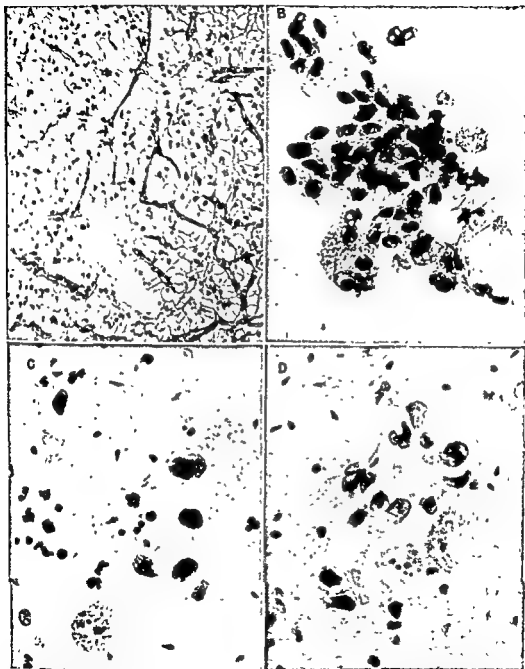


FIG A Renal adenocarcinoma (clear cell) which gave rise to cells in urinary sediment illustrated in figures B, C and D

FIG B Smear of urinary sediment (routine hematoxylin-eosin stain) showing neoplastic cells of tubular adenocarcinoma in figure A

FIGS C AND D Section of paraffin block of sediment of urine from the patient with the adenocarcinoma of figure A showing neoplastic cells and, incidentally, spermatozoa



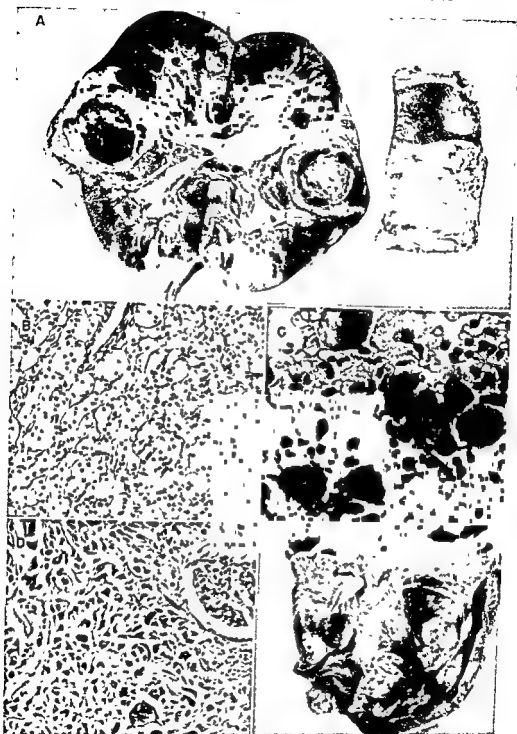


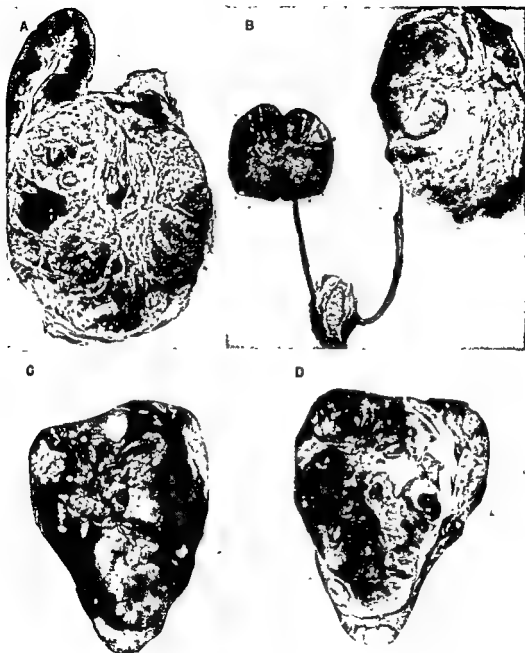
FIG A Small adenocarcinoma of the kidney which, despite its size, yielded enormously widespread metastases including some to the myocardium (figure E) The central portion of the tumor is of the clear cell variety, the rim is made up of highly anaplastic sarcomatous cells The latter were responsible for most of the metastases The vertebrae pictured beside the kidney contain metastatic deposits

FIG B Clear cell component of the adenocarcinoma in figure A

FIG D Spindled carcinomatous component from the periphery of the tumor in figure A

FIG C Aspiration smear from a vertebra showing metastatic renal carcinoma from lesion of figure A

FIG E Extensive metastases to the heart from the small tumor in figure A



*Wilms' tumors of infants showing cystic, trabecular, hemorrhagic and solid fleshy variations in structure, along with pseudocapsules*

and consist of *lipomas, fibromas, angiomas, leiomyomas, adenomas*, as well as complex mixtures of the various elements of such growths (plates 282, 283). In some cases, the pyelograms of these kidneys may be mistaken for polycystic disease (Melecos). Rarely sarcomatous change occurs but metastases have not been recorded as far as we are aware. Rarely, too, the tumors may be large and may thereby interfere with renal function. In addition, rhabdomyomas of the myocardium or glycogen masses simulating rhabdomyomas, are found with tuberous sclerosis.

*Lindau's disease* consists of angiomas of the retina (or von Hippel's disease) and cerebellum, associated with syringomyelia, hydromyelia, cysts of the liver, pancreas and kidney, and angiomas, adenomas or carcinomas of the kidney (Davison et al.).

### *Parenchymal Sarcomas*

Exclusive of the Wilms' tumors which are often called adenosarcomas, sarcomas of the renal parenchyma are rare. The reports would be even more scarce if sarcomatoid, spindle cell, anaplastic carcinomas, the lymphomas, and Wilms' tumors that masquerade as uniform spindle cell sarcomas in a given section, were properly pruned from these reports. Moreover, some of the reported fibrosarcomas are, in reality, leiomyosarcomas, and liposarcomas may be erroneously labeled fibrosarcomas, fibromyxosarcomas or myxosarcomas, round cell sarcomas may actually be lymphomas, embryonal myosarcomas, or anaplastic carcinomas. Occasionally Wilms' tumors of adults may present themselves as predominantly leiomyosarcomatous. In 1932, Judd and Donald reported 20 histologically documented cases of sarcoma (3.5 per cent) in a series of 570 renal cancers. Eight others were suspected of being sarcomas, but histologic proof was lacking. The tumors of children were excluded from these 28 cases.

The diagnoses included. fibrosarcoma (6), sarcoma, type undiagnosed (6), spindle cell sarcoma (3), round cell sarcoma, liposarcoma, myxosarcoma, fibromyxosarcoma, mixed-cell sarcoma, and fibrosarcoma-adenocarcinoma (1 each). Sarcomas of the adult kidney metastasize with great rarity although they may reach a huge size, and thereby add to the operative hazard.

### RENAL ADENOCARCINOMA

#### *Definition*

The term renal adenocarcinoma is used here instead of hypernephroma or Grawitz tumor. It is now reasonably clear that this neoplasm, with possibly rare exceptions, arises from the tubular epithelium, usually beginning as an "adenoma," rather than from adrenal rests residing within the parenchyma of the kidney. The qualifying terms *granular cell, clear cell, spindle cell* or *heterocellular adenocarcinoma* now often appear artificially and insignificantly distinctive, although perhaps some such differentiation may ultimately be paralleled with a biochemical or functional counterpart.

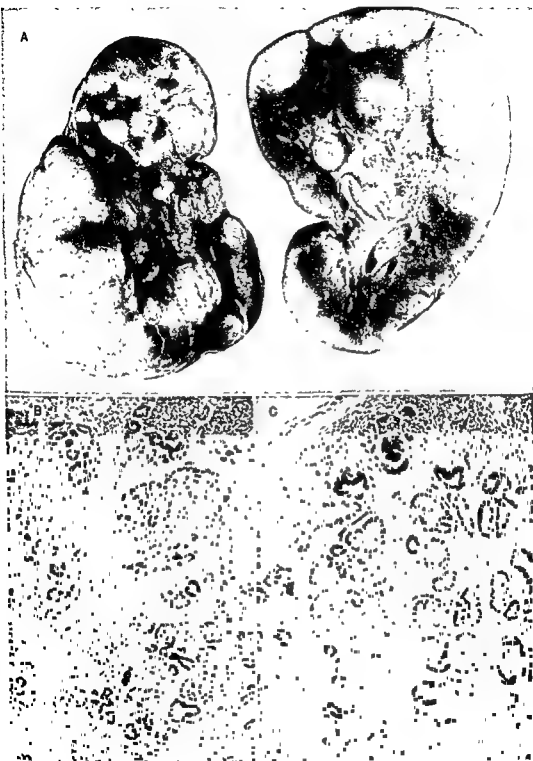
#### *Incidence*

The parenchymal adenocarcinomas comprise 9 out of every 10 malignant tumors of the kidney and about 3 per cent of visceral cancers. These tumors occur predominantly in the sixth and seventh decades, and rarely before the age of 30. For reasons altogether unclear, there is a distinct preponderance of these tumors among males, a ratio of approximately 7 to 3 (Priestley). If the adenocarcinomas represent a degeneration of an adenoma, it would be expected that there would be a corresponding predominance of such adenomas in males. Actually the over-all incidence of the adenomas is more common in males (Leary, Cristol et al.). In Cra-

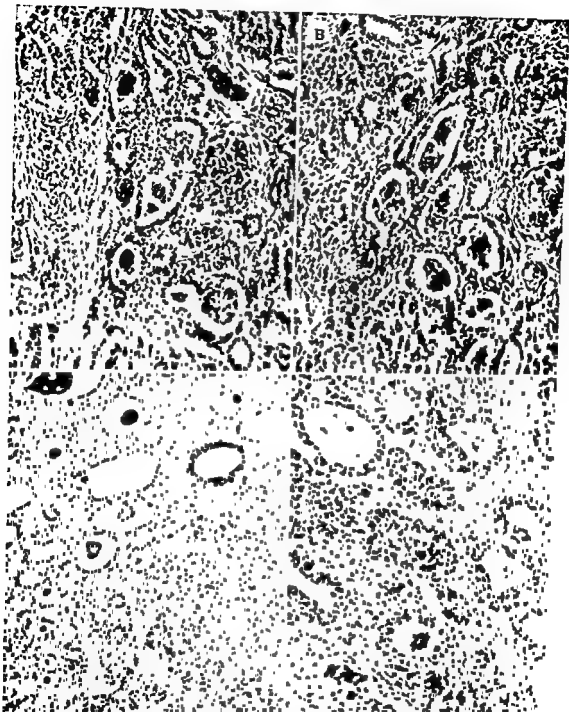
FIG A Wilms' tumor showing peripheral distribution of the neoplastic tissue corresponding to the peripheral distribution of the actively proliferating portion of the metanephrogenic renal blastema (figure C)

FIG B Wilms' tumor of figure A, illustrating the close resemblance of the neoplastic tissue to the renal blastema

FIG C Embryonic kidney of 3 cm fetus showing the similarity of the peripheral, multipotent cells to those of the Wilms' tumor.

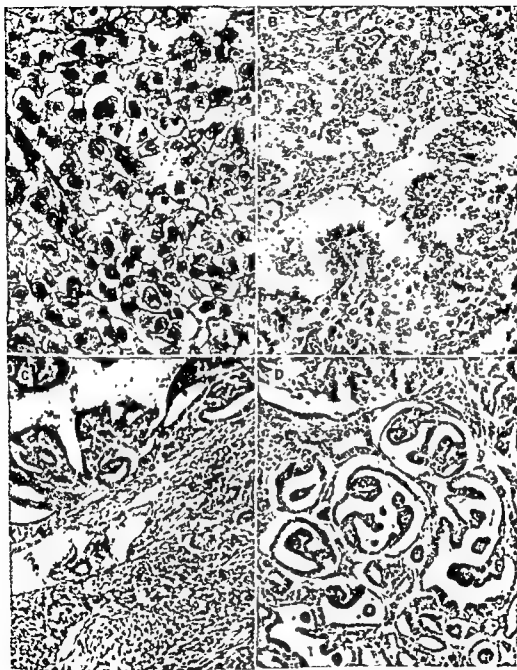


(Legends on facing page)



FIGS A AND B *Pseudoglomerular structures and calcific concretions in a Wilms' tumor characterized by a prominent epithelial component. There are many tubules, some partially invaginated simulate embryonic glomeruli, others of small size may be confused with rosettes. Calcification may be sufficiently marked to be visible in a roentgenogram.*

FIGS C AND D *Pseudoglomerulus in a Wilms' tumor. In this instance, the pseudoglomerulus is the result of invagination of a neoplastic tubule by the peritubular sarcomatous element. There is some similarity between the pattern of development of these pseudoglomeruli from the neoplastic tubules and the normal pattern of fetal development of glomeruli (plate 226C).*



*Histologic variations in Wilms' tumors*



FIG A Wilms' tumor made up of solid, resilient, partially chondrified tissue

FIG B Islet of cartilage in a Wilms' tumor simulating squamous cell epithelium

FIG C Intimate admixture of hyaline cartilage and other neoplastic elements in a Wilms' tumor. The hyaline cartilage appears to have been formed by metaplasia of neoplastic cells rather than as a result of dysontogenetic chondral rests of the sort illustrated in figure A, plate 300

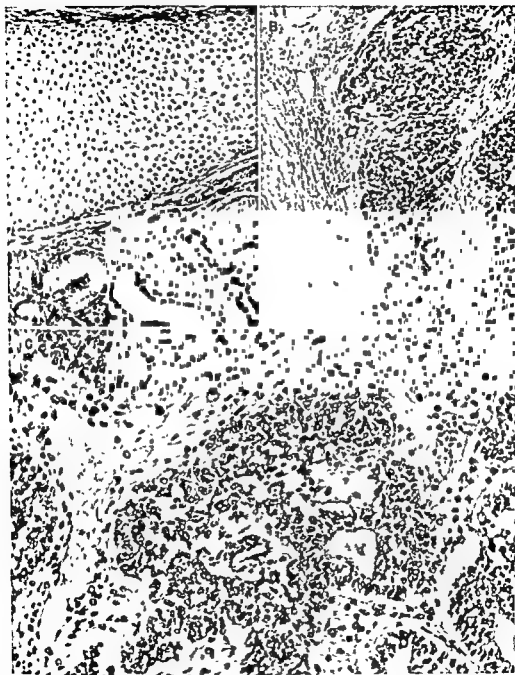


FIG. A Benign chondral rest in the medulla of otherwise normal kidney of an infant

FIG. B Pseudocapsule at the periphery of a Wilms' tumor

FIG. C Abortive tubular formation in a Wilms' tumor. This pattern resembles the multipotent tissue present at the periphery of an embryonic kidney





FIG. A Wilms' tumor made up of solid, resilient, partially chondrified tissue

FIG. B Islet of cartilage in a Wilms' tumor simulating squamous cell epithelium

FIG. C Intimate admixture of hyaline cartilage and other neoplastic elements in a Wilms' tumor. The hyaline cartilage appears to have been formed by metaplasia of neoplastic cells rather than as a result of dysontogenetic chondral rests of the sort illustrated in figure A, plate 300

PLATE 300. MALIGNANT NEOPLASMS WILMS' TUMOR

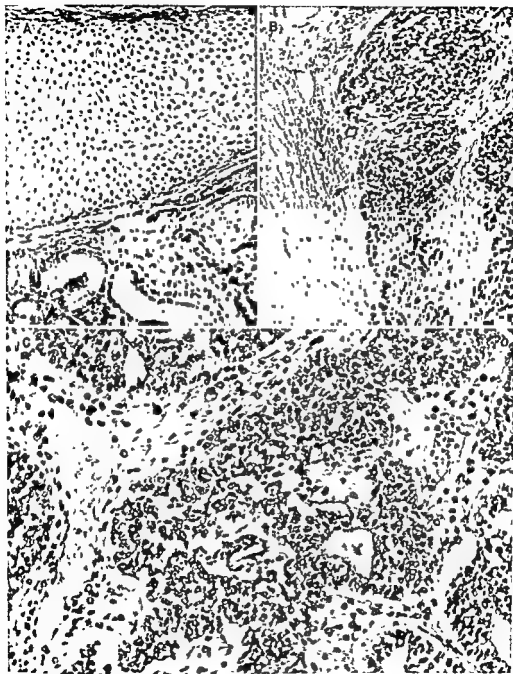


FIG A Benign chondral rest in the medulla of otherwise normal kidney of an infant

FIG B Pseudocapsule at the periphery of a Wilms' tumor

FIG C Abortive tubular formation in a Wilms' tumor This pattern resembles the multipotent tissue present at the periphery of an embryonic kidney

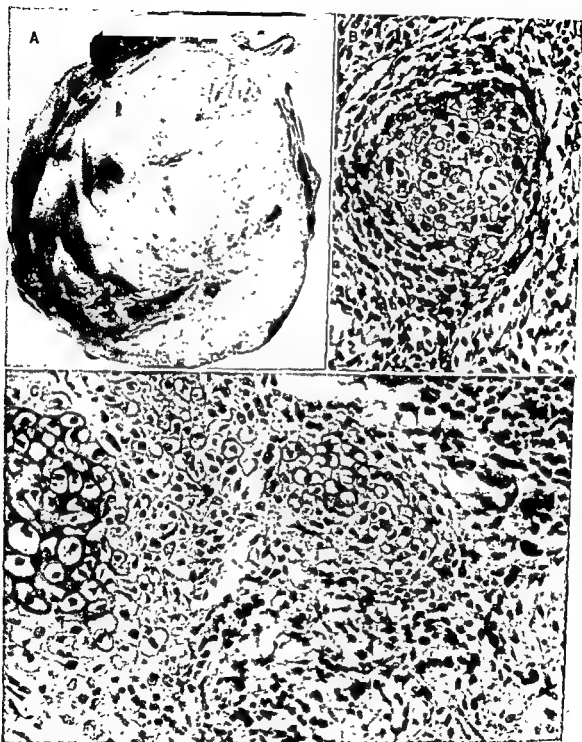


FIG A. Wilms' tumor made up of solid, resilient, partially chondrified tissue

FIG B. Islet of cartilage in a Wilms' tumor simulating squamous cell epithelium

FIG C. Intimate admixture of hyaline cartilage and other neoplastic elements in a Wilms' tumor. The hyaline cartilage appears to have been formed by metaplasia of neoplastic cells rather than as a result of dysontogenetic chondral rests of the sort illustrated in figure A, plate 300

PLATE 300. MALIGNANT NEOPLASMS: WILMS' TUMOR

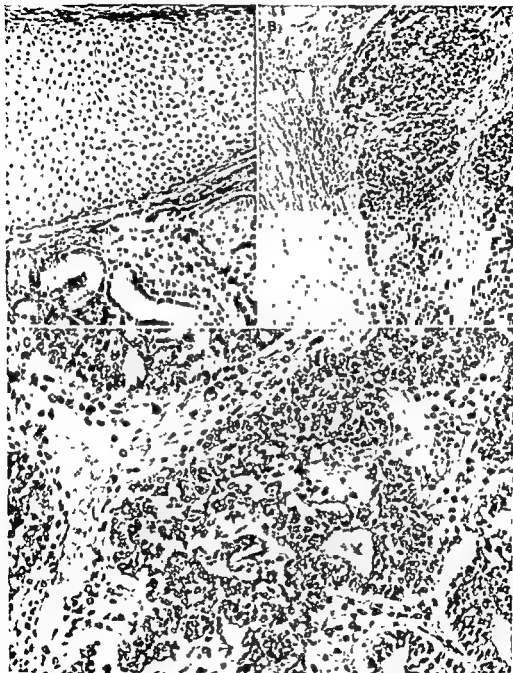


FIG A. Benign chondral rest in the medulla of otherwise normal kidney of an infant

FIG B Pseudocapsule at the periphery of a Wilms' tumor

FIG C Abortive tubular formation in a Wilms' tumor. This pattern resembles the multipotent tissue present at the periphery of an embryonic kidney

tol's series, the incidence of adenomas was 5.8 per cent in males, as against 1.3 per cent in females.

In a remarkably high number of cases, the initial symptoms, unfortunately, are not caused by the direct mechanical or invasive effects of the primary tumor, but by its metastases to lungs and bones. Astonishing instances of regression of pulmonary metastases following the removal of the primary renal adenocarcinoma have been reported (Mann, Bumpus, Willis). There appears also to be adequate justification for removal of a single metastasis after the primary tumor is controlled even if it requires a pulmonary lobectomy, as the case of Barney and Churchill proves.

In Priestley's series of 302 adenocarcinomas, 47.7 per cent survived more than 3 years, 35.4 per cent more than 5 years and 27.8 per cent more than 10 years. This survival rate is much greater than that for the carcinomas of the renal pelvis, particularly the nonpapillary ones.

The renal carcinomas frequently metastasize to lungs (57 per cent), bones (32 per cent), regional lymph nodes (41 per cent), liver (27 per cent) and adrenals (11 per cent). From about 8 to 18 per cent of renal adenocarcinomas metastasize to the opposite kidney, a feature that must be evaluated carefully in the determination of independent bilateral origin of these tumors. Other organs to which metastases seed are brain, thyroid, heart, peritoneum, spleen, skin and ureter. Odd locations for metastases are also often selected, such as the tonsil, larynx and iris.

### *Pathology of Renal Adenocarcinoma*

#### *Gross appearance*

The primary renal adenocarcinoma may come to occupy any portion of the parenchyma, the poles or the central portion, and varies in size from 3 cm. to huge dimensions. However, the small tumors arise almost exclusively in the cortex. The largest in Bell's series weighed 3300 Gm. The diameter of 3 cm. is arbitrarily selected by Bell as the borderline between the benign tubular adenoma and the adenocarcinoma because only one of 45 tumors less than 3 cm. proved malignant. Actually, tumors less than 5 to 6 cm. in diameter rarely yield metas-

tases. At this size, however, it may be impossible to be certain from the gross or even the microscopic examination if the tumor is cancerous or benign. Obviously, such arbitrary criteria of malignancy serve merely as a presumptive, exceedingly rough guide and are no more reliable for individual cases than is the use of 2.5 cm. as a criterion for judgment of the malignancy of gastric ulcers.

Renal adenocarcinomas (plate 234) are spherical or bosselated and moderately soft. On section they are bright yellow, and, especially in the larger tumors, mottled with deep red hemorrhagic and necrotic areas, and grey areas of fibrosis. The smaller tumors appear deceptively encapsulated, the larger ones invade the adjacent parenchyma and perarenal tissues, and show a particular propensity for entering the renal vein and extending in continuity up the inferior vena cava to the right heart. Because the tumor may invade the renal vein as a solid cast prior to distant metastasis, surgeons must remove this tongue of tumor, even if it extends into the inferior vena cava, occasionally with gratifying results.

#### *Histologic appearance of renal adenocarcinoma*

The histologic details are illustrated in plate 285 to 294. As with the adenomas, the cells frequently resemble tubular epithelium closely. Some of the tumors are made up entirely of clear cells with small uniform nuclei and cytoplasm containing lipid with vitamin A (Papanicolaou) (plate 289), more or less glycogen, and unstainable hydropic vacuoles. The content of vitamin A is demonstrable with fluorescent microscopy. Other adenocarcinomas have clear cells mixed with granular cells (plates 285, 286, 287), and still others have components of virulent spindle cells (plate 294D) that are truly altered carcinomatous cells but may be mistaken for sarcoma or a variant of Wilms' tumor. The granular cells are postulated by Melicow as being derived from the visceral or parietal glomerular epithelium or from granular cell adenomas. There is little to support the theory of origin of these tumors from Bowman's epithelium. Occasional cells have inclusions of hyaline droplets, hemosiderin and lipochrome.

PLATE 301. MALIGNANT NEOPLASMS: WILMS' TUMOR

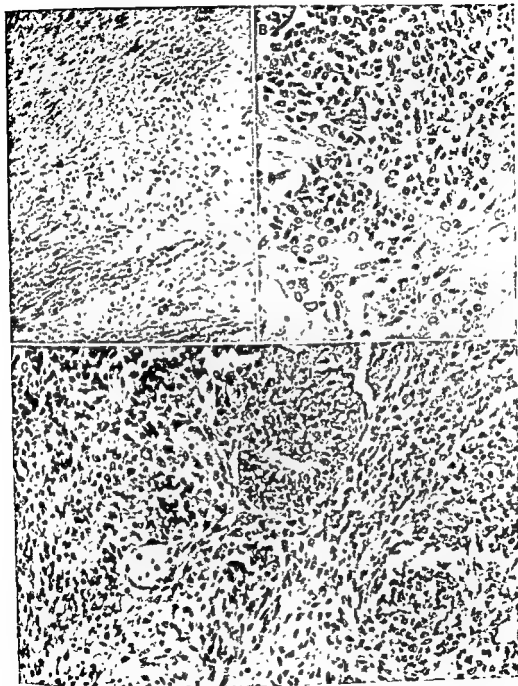
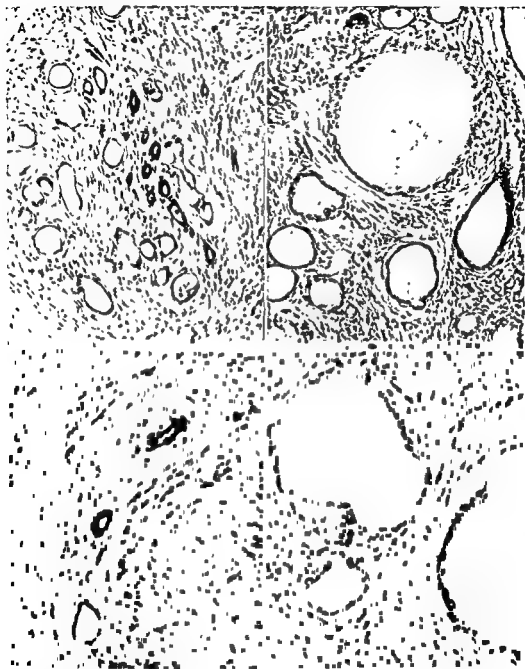


FIG A Well differentiated sarcomatous element in Wilms' tumor with desmoplasia and focal fatty degeneration. The field was representative of most of the tumor which nevertheless metastasized widely. See figure B.

in the primary neoplasm

FIG C The epithelial and mesenchymal variation in this portion of a Wilms' tumor is suggestive of the similar normal variations at the peripheral capsule of tissue of the embryonic kidney.





FIGS A AND B Microcystic and desmoplastic changes after irradiation. The dilated tubules represent viable tumor

FIGS C AND D Spontaneous cystic change in Wilms' tumor which might be mistaken for a polycystic kidney in a biopsy specimen



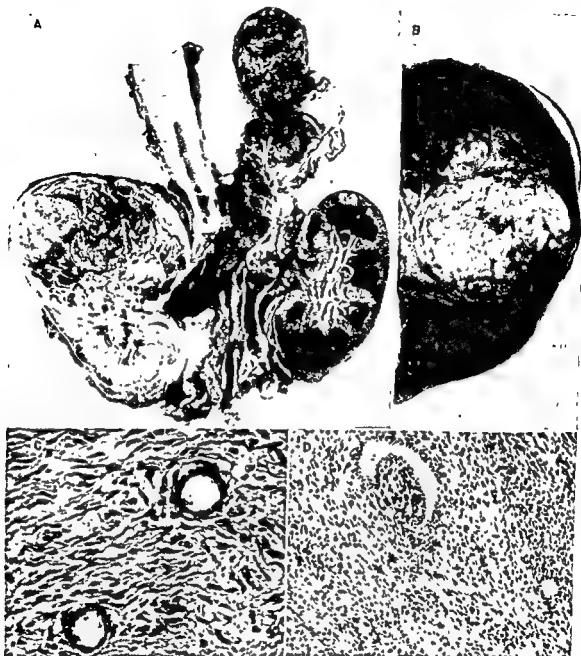


FIG A Venous invasion (tumor thrombus) from Wilms' tumor of the right kidney extending into renal vein and inferior vena cava. Pulmonary metastases were present

FIG C Two tubules with single layered epithelium caught in the sarcomatous element of Wilms' tumor

FIG B Small Wilms' tumor discovered incidentally in the kidney of a 32 year old male who died from malignant nephrosclerosis (photomicrograph in figure D)

FIG D Adenosarcomatous features of Wilms' tumor of figure B

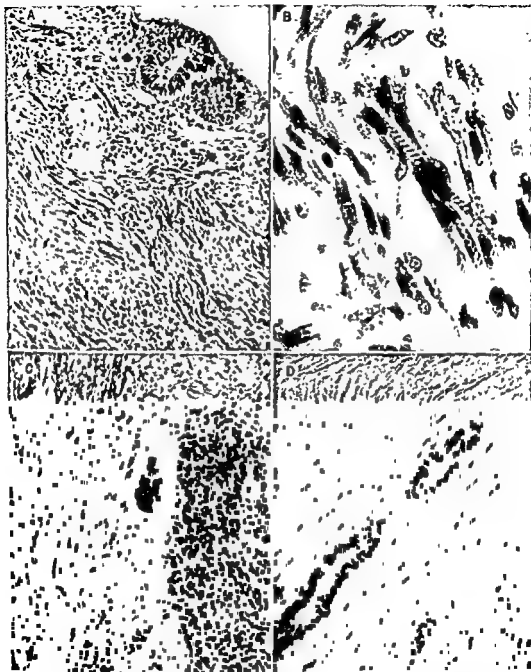


FIG A Prominent muscle component in a Wilms' tumor

FIG B Cross striations in muscle fibers in a Wilms' tumor (Masson trichrome stain)

FIG C Muscle cells in association with masses of neoplastic cells simulating lymphocytes in a Wilms' tumor

FIG D Deceptively torpid and non-neoplastic appearance in portion of a Wilms' tumor

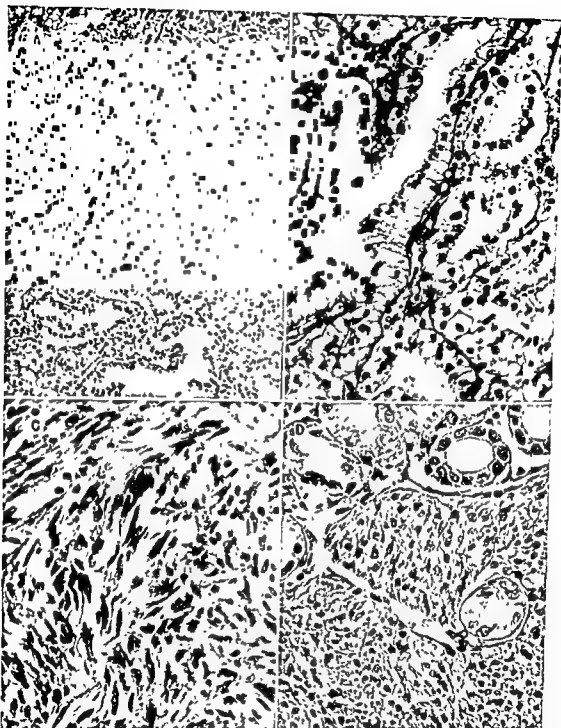


FIG. A Carcinosarcoma of a kidney composed of two fairly pure components (1) leiomyosarcoma and (2) clear cell carcinoma. This case is from an adult.

FIG. B Higher magnification of the clear cell carcinomatous element in figure A. The clear cell component may be so conspicuous as to lead to the erroneous diagnosis of a simple clear cell carcinoma or hypernephroma in children.

FIG. C Myosarcoma of kidney considered by many to be a variant of Wilms' tumor. Muscle striations were present.

FIG. D Large pure leiomyosarcoma of kidney.

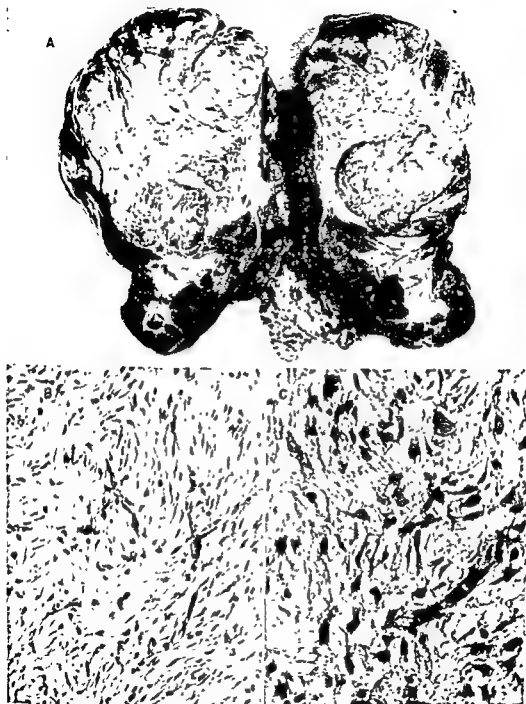


FIG. A. *Myosarcoma of the kidney in a 32 year old patient resulting in death from massive local recurrence*

FIGS. B AND C. *Loosely edematous myosarcoma of kidney illustrated above. Some observers regard renal parenchymal myosarcoma as a one-sided development of a Wilms' tumor*

granules which suggest even a functional resemblance to renal tubular epithelium

The patterns are as variable as the cells and include solid, alveolar, papillary, tubular and cystic arrangement. Large, thin-walled sinuses ready to receive invading cells (plate 292A) are a characteristic feature of this tumor. Foci of necrosis, calcification, desmoplasia, and old and recent hemorrhage vary the picture. The spotty calcification may be visible in roentgenograms, and may be of diagnostic assistance, although it must be remembered that about 15 per cent of simple cysts show evidence of calcification (Cahill and Melicow). Attempts to gauge the prognostic significance of the different patterns and types of cells are not reliable, although the virulent sarcomatoid cells may be expected to metastasize early and extensively. The size of the tumor is the principal factor in prognosis, although, again, exceptions do occur (plate 294)

### WILMS' TUMOR

#### *Incidence, diagnosis and therapy*

Wilms' tumors constitute about 20 to 25 per cent of all malignant neoplasms of childhood, it is second in frequency to the neuroblastomas, according to Wells and most other observers. The Wilms' tumors are practically the only malignant tumors of the kidney in this age group. Of 16,565 admissions for cancer to the Memorial Hospital, 0.1 per cent were for these tumors. The majority of Wilms' tumors are observed before two years of age, about 90 per cent of them occur during the first seven years of life. Undoubtedly some instances of reported "hypernephroma" in infancy represent variants of Wilms' tumor. It is stated that an analogous neoplasm is the commonest tumor of swine (Kretschmer and Hibbs), this latter neoplasm, however, rarely produces metastases. Any tumor of the abdomen in children should be considered to be a Wilms' tumor until proved otherwise. Neuroblastoma of the adrenal, em-

bryonal rhabdomyosarcoma, unilateral polycystic kidneys and unilateral hydronephrosis may simulate Wilms' tumor.

The visible and palpable mass may be the only symptom of the tumor and in most cases antedates pain and hematuria; the latter may not appear at all because of the failure of the tumor to communicate with the pelvis or tubules. Wilms' tumors occur on either side with equal frequency and, unlike other malignant renal tumors, there is no sex predisposition. The tumors grow rapidly, metastasize and cause death usually within a few months after discovery in most untreated cases. Metastases occur chiefly in the liver, lungs and regional lymph nodes, but may involve the brain, adrenals and other organs. The treatment of choice currently is nephrectomy supplemented with x-radiation. The matter of the use of x-radiation pre- and/or postoperatively, is handled differently in the various centers. The radiosensitivity varies markedly and apparently is dependent on the histologic structure of this highly variegated tumor (Kretschmer). Preoperative x-radiation certainly decreases the size of some of the tumors remarkably, thus facilitating the operative procedure.

If recurrences are to take place, they generally do within the first two years after operation, although latent periods of ten years have been recorded. Five year cures are estimated at between 10 and 15 per cent (Hyman, Priestley and Schulte).

Although Wilms' tumors are principally tumors of childhood, they are not extremely rare in adults. Sparks collected 26 cases in the literature up to 1942. Rarely, they are found incidentally at autopsy, as in the instance of the small one illustrated in plate 304B, which, although histologically malignant, had not yet metastasized. This patient was a 32 year-old man who died of uremia with malignant hypertension. The small size of the tumor and its out of the way cortical position suggested no relationship to the hypertension.

---

FIG. A *Angiomyomatous polyp* at ureteropelvic junction. These were ball-valve in action, blocking the ureteral catheter, but not the urinary outflow.

FIG. B *Section of angiomyomatous polyp* from figure A. The whorls of muscle about the vessels resemble the pattern of the angiomyoma of the skin.



(Legends on facing page)

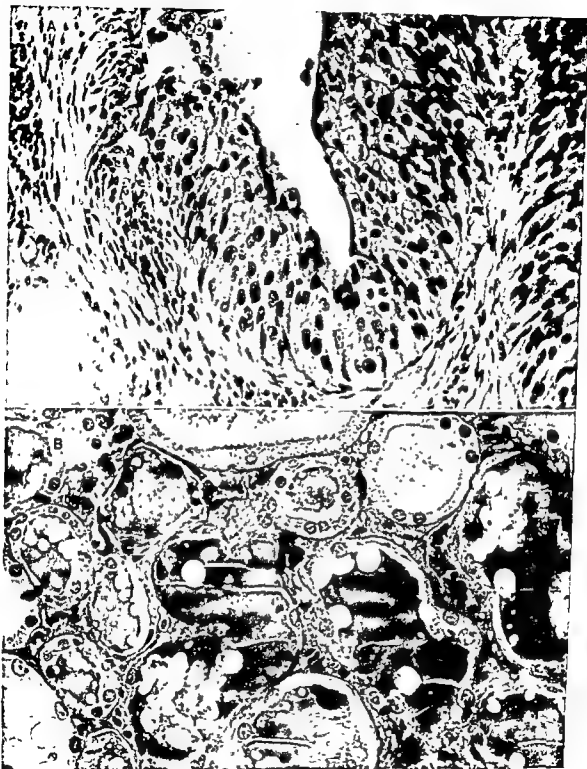


FIG A Noninfiltrating epidermoid carcinoma (carcinoma in situ) of pelvic epithelium

FIG B Regenerating large hyperchromatic tubular cells, from a case of acute glomerulonephritis, which could easily be confused with neoplastic cells in a smear of urinary sediment.

A

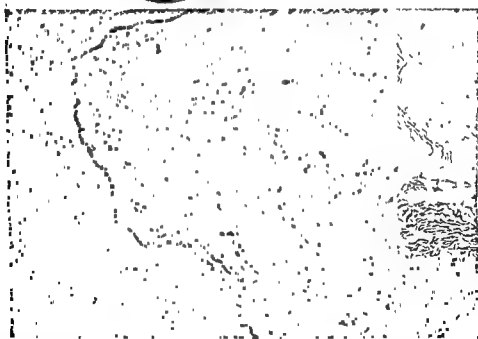


FIG A *Leukoplakia of pelvis and calyces*. No calculi were present. Section illustrated in figure III (AFIP Acc 17372)

FIG B *Keratinization of epidermalized calyceal mucosa* from kidney illustrated in figure A. No dyskeratosis or anaplasia is included in this highly differentiated squamous epithelium. The squamous metaplasia of the pelvic mucosa following infection or irritation by calculi, rarely produces this degree of keratinization and the cells are usually less differentiated. However, leukoplakia of the renal pelvis, with or without squamous cell metaplasia, is prone to undergo carcinomatous transformation (compare plates 309A and 311A)



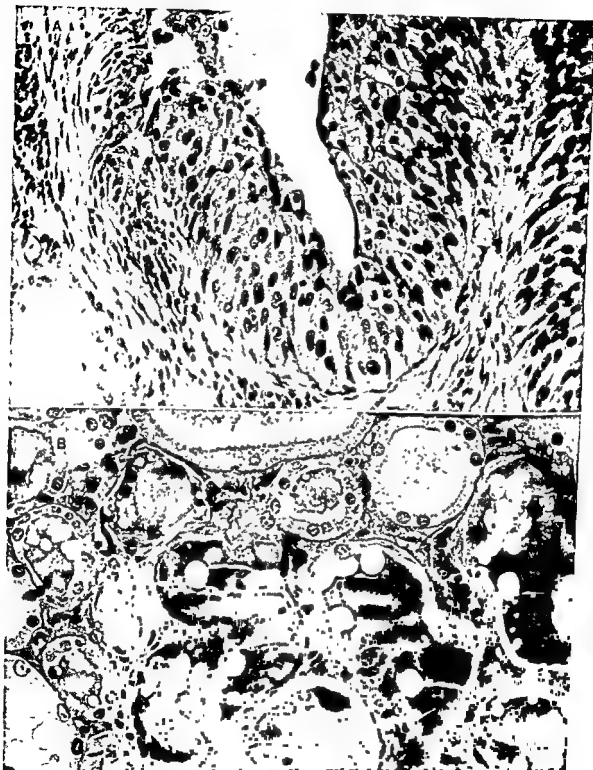


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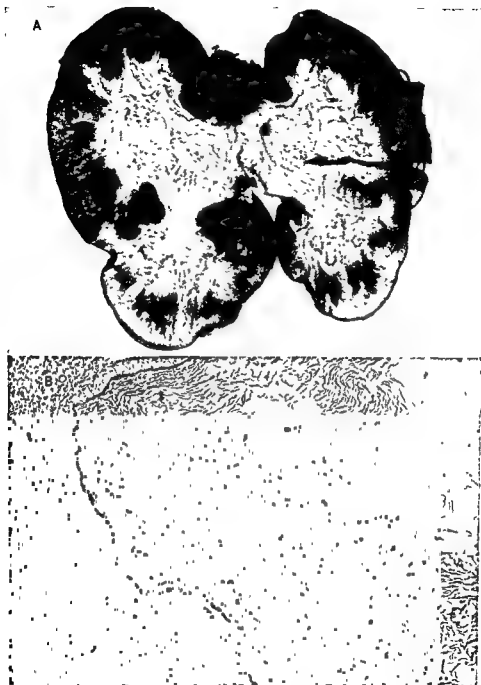


FIG. A. *Leukoplakia of pelvis and calyces.* No calculi were present. Section illustrated in figure B (A.F.I.P. Acc. 17372).

FIG. B. *Keratinization of epidermalized calyceal mucosa from kidney illustrated in figure A.* No dyskeratosis or anaplasia is included in this highly differentiated squamous epithelium. The squamous metaplasia of the pelvic mucosa following infection or irritation by calculi, rarely produces this degree of keratinization and the cells are usually less differentiated. However, leukoplakia of the renal pelvis, with or without squamous cell metaplasia, is prone to undergo carcinomatous transformation (compare plates 309A and 311A).



FIG A. *Leukoplakia* of renal pelvis with epidermalization, from a case of calculous pyelonephritis

FIG B *Epidermoid carcinoma* from leukoplakic pelvis illustrated in figure A. The carcinoma is so anaplastic that it might easily be mistaken for a metastasis or a variant of a Wilms' tumor

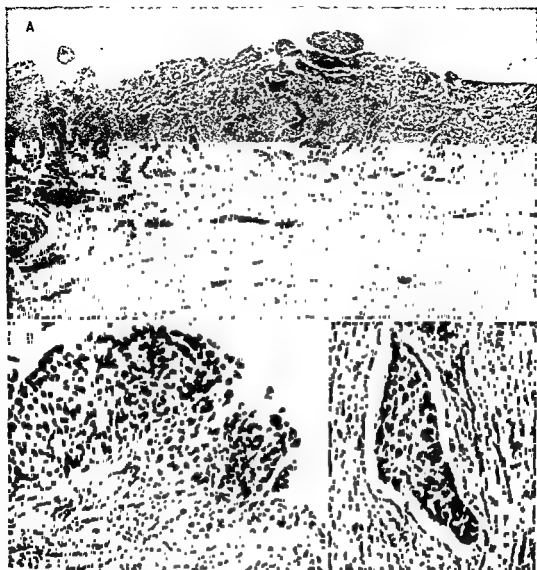


FIG. A. Papillary epidermoid carcinoma of renal pelvis with extension to ureters and bladder. A nest of tumor is present in a lymphatic vessel at the left.

FIG. B. Higher magnification of the papillary epidermoid carcinoma of figure A. The neoplasm in this field appears deceptively noninvasive.

FIG. C. Pelvic lymphatic invasion of the papillary epidermoid carcinoma illustrated in figures A and B.

### *Pathology of Wilms' Tumor*

#### *Gross appearance*

The tumor may be situated in the center or at the poles of either kidney, or may replace the cortical area and rim the kidney (plates 295, 296A). Primary bilateral involvement rarely occurs. Small Wilms' tumors are rarely seen; the small one pictured in plate 304B is exceptional, as stated. The tumors generally are circular, expanding masses with a pseudocapsule. The tumors may reach huge proportions; several cases weighing 7 to 12 pounds have been reported and one weighing 30 pounds is described (Neff). They may compress the kidney markedly with resultant destruction of a considerable portion of the renal parenchyma.

The sectioned surfaces of the tumors are usually variegated so as to resemble ordinary teratomas, with irregular, solid and gelatinous, cystic and hemorrhagic areas (plate 295). Some, however, are as homogeneously fleshy as leiomyosarcomas (plate 299A).

#### *Histologic appearance of Wilms' tumor*

The histologic variations in the Wilms' tumors are about as extensive as they are in teratomas of the testis. This feature is illustrated in plates 296 through 306. The element that has come to be recognized as the pivotal histologic feature of the Wilms' tumor is the abortive glomerulo-tubular structures with immature, hyperchromatic spindle cell stroma also known as "renal blastema" (plate 296B). These structures are more or less faithful modifications of glomerulo-tubular anlagen that can be seen in the subcapsular portions of kidneys of young human embryos (plate 296C). These same structures are the essential reason for the use of "adenosarcoma" as a synonym for Wilms' tumor although often there are more overt sarcomatous components. It might perhaps be added that the neoplasm labelled "glomeruloma" (Owen) has no relationship to Wilms' tumor. The justification of this designation on the basis of the evidence thus far advanced is not convincing. In Owen's case, the history of a previously resected carcinoma of the breast and the lack of an autopsy somewhat weaken the nosological position of the new term.

In addition to the haphazardly scattered proliferations of glomerulo-tubular structures, there are these other elements seen in Wilms' tumors: (1) foci indistinguishable from leiomyosarcoma, (2) foci of distinctly striated muscle which are present in a large percentage of Wilms' tumors (plate 305 B), (3) tubular cysts (plate 303), (4) fibromatous areas (plates 301A, 303D), (5) collections of small hyperchromatic cells that simulate neuroblastomas including rosettes (plates 297A, B; 333D), (6) chondral and osseous foci (plate 299), and (7) areas of degeneration including dense fibrosis, necrosis and lipid histiocytes (plates 301A, 302B).

*Metastases* may look entirely different from the primary tumor (plate 301A, B). This phenomenon is not unexpected in view of the kaleidoscopic composition of many of the primary tumors. As with other composite tumors, the most anaplastic element is likely to metastasize first and most abundantly. There are exceptions to this rule, but it is clear that differences in radiosensitivity between the primary Wilms' tumor and its metastases are not unexpected. A single section of the primary tumor may reveal no area that resembles the metastases. Another feature of the Wilms' tumor that merits emphasis is that fibrosis, deposition of lipid macrophages and necrosis may occur spontaneously and so simulate changes attributable to x-radiation (plate 302).

As indicated, the prognosis in cases of Wilms' tumor is grave. It is hazardous to evaluate the prognosis on the basis of the histologic pattern of these neoplasms, especially if there is the temptation to be optimistic because of a relatively benign appearing cellular composition. The presence of venous invasion within the kidney is always an ominous sign.

#### *Embryogenesis*

The Wilms' tumor has been responsible for an abundant, necessarily speculative literature dealing with the embryogenesis or possible anlage of the various components of the tumor. Individual theories have been constructed on the basis of preferential emphasis on the significance of the separate neoplastic elements or on the basis of inferences drawn from the association of two or more of such elements. For

PLATE 313. MALIGNANT NEOPLASMS: PAPILLARY EPIDERMOID CARCINOMA

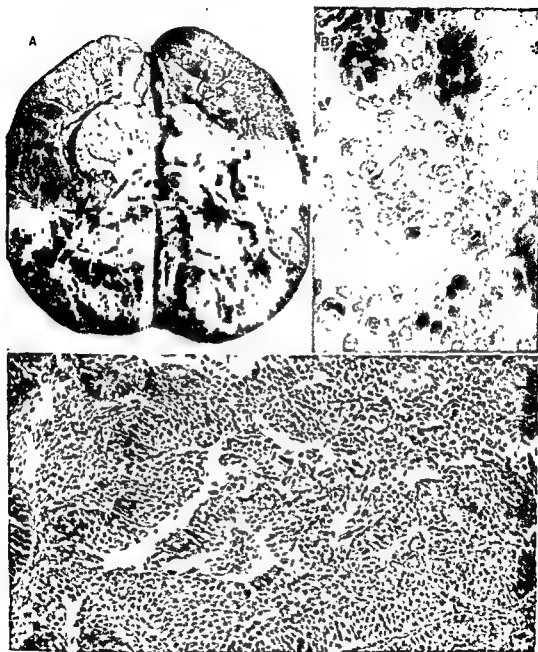
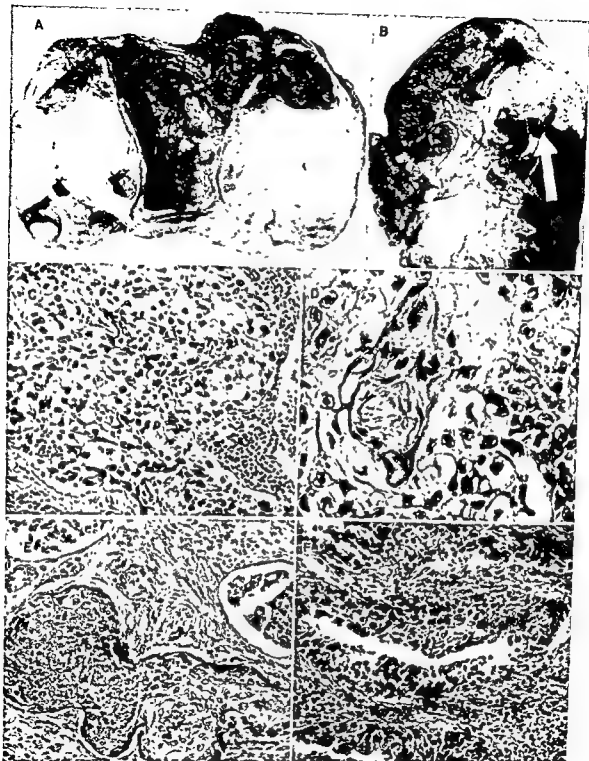


FIG. A. Papillary epidermoid carcinoma of renal pelvis. This neoplasm has grown out into the pelvis and infiltrated only superficially in contrast to those in plates 311 and 314.

FIG. B. Smear of papillary epidermoid carcinoma of figure A stained with hematoxylin-eosin. A mitotic figure is included (arrow).

FIG. C. Papillary epidermoid carcinoma of figures A and B.



FIGS A AND B Virulent infiltrating nonpapillary epidermoid carcinoma arising from calyceal epithelium

FIGS C AND D Infiltrating epidermoid carcinoma arising from calyceal epithelium.

FIG E Intrarenal lymphatic invasion by epidermoid carcinoma of renal pelvis

FIG F Squamous metaplasia in collecting tubules



FIG. A. *Mucous adenocarcinoma of renal pelvis* (Histologic slide through courtesy of Dr. A. B. Higgins.)

FIG. B. *Mucous adenocarcinoma of renal pelvis*. The histologic picture is indistinguishable from that of colonic mucosa. (Histologic slide through courtesy of Dr. L. V. Ackerman.)



A



B



C



FIG A Peripelvic lymphatic cysts (Courtesy of Drs Joseph F Kuzma and W A D Anderson )

FIG B Old hemorrhage into solitary cyst of kidney  
The hemorrhage followed attempted aspiration of  
the cyst eight years previously

FIG C Perirenal hematoma from rupture of athero-  
sclerotic aorta



FIG. A. Pararenal liposarcoma, weighing approximately 1400 Gm.

FIG. B. Section from liposarcoma of figure A, showing adult fat cells and hyperchromatic lipoblasts resembling fibroblasts.

FIG. C. Another field from liposarcoma of figure A, in which an abortive Touton giant cell showing anaplasia is seen.

example, the presence of striated muscle, smooth muscle, and cartilage has influenced thought in the direction of the origin of Wilms' tumors from the myotome. The presence of actual and simulated nerve elements has won advocates to the neurogenous theory of the nature of many Wilms' tumors. However, the concept that seems more often and more completely in harmony with the histologic facts attributes the genesis of the Wilms' tumor to the renal blastema, that is, to a neoplastic change in the renal anlage. Because of the close simulation of the histological pattern of many Wilms' tumors to that of the nephrogenic cap (plate 296B, C) the impression of histogenetic relationship is easily achieved. Moreover, occasionally a Wilms' tumor traverses the cortex much after the fashion of a nephrogenic cap (plate 296A).

The origin of the Wilms' tumor is not the same as that of the organoid teratoma. Wilms' tumor clearly is of mesenchymal origin. The teratoma, as it is generally defined, is a rare renal tumor derived from the three germ layers, endoderm, mesoderm and ectoderm, and may include such structures as brain and intestines (Lubarsch).

### TUMORS OF THE RENAL PELVIS

It is estimated that about 5 to 10 per cent of clinically apparent renal tumors are of the renal pelvis, and that malignant tumors of the renal pelvis are found in about 0.5 per cent of autopsies (Bell). These are divided approximately as follows:

Papilloma	30%
Papillary transitional cell, epidermoid or squamous cell carcinoma	45%
Nonpapillary transitional cell, epidermoid or squamous cell carcinoma	25%
Mucous adenocarcinoma	rare

The majority of cases occurs between 40 and 60 years of age, although cases in infancy have been reported. The predominance in the male of renal pelvic neoplasms, both papillary and nonpapillary, is somewhat greater than for the parenchymal tumors and is of the order of 2:1 to 3:1. The outstanding symptom is hema-

turia, usually intermittent, often gross and occasionally with clots. Pain is not a prominent symptom. A local mass may be palpable generally not because of the pelvic neoplasm but as a result of the obstructive hydronephrosis. The association of renal pelvic tumors, especially nonpapillary carcinomas, with calculi and infection is common (Kretschmer). Calculi and infection lead to, or are at least associated with, leukoplakia of the renal pelvis. Leukoplakia of the renal pelvis, as in the case of other mucous membranes, frequently precedes the development of carcinoma (plates 310A, 311A).

### Special features

There are two features of tumors of the renal pelvis that deserve special emphasis.

1 Papillary carcinomas may appear deceptively benign, and

2 Papillary neoplasms of the renal pelvis are commonly associated (from 28.8 to 50 per cent, Cabot and Allen; Caulk) with similar tumors in the ureter and bladder, and may be bilateral. In other words, the finding of a papillary tumor of the bladder, especially near *either* ureteral orifice is sufficient basis to search for similar tumors in *either* of the ureters and renal pelvis. The reason for the association is probably a neoplastic diathesis of the mucosa of the urinary tract with multicentric origin of the tumors, rather than implantation through direct or lymphatic seeding. In any case, the multiplicity of the papillary lesions in the renal pelvis and ureter is so frequent that nephrectomy for pelvic tumors should be accompanied by total ureterectomy, preferably with removal of a cuff of bladder about the ureteral opening. The association of pelvic, ureteral and bladder lesions is uncommon in the case of nonpapillary carcinomas of the renal pelvis and in renal parenchymal tumors.

### Prognosis

The main renal vein, its principal tributaries and the lymphatics are involved in a high percentage of cases. Such involvement appreciably worsens the prognosis, as does a high histologic grade of the tumor. Arterial invasion is rare.

The prognosis of the papillary tumors without apparent infiltration is poor enough to em-

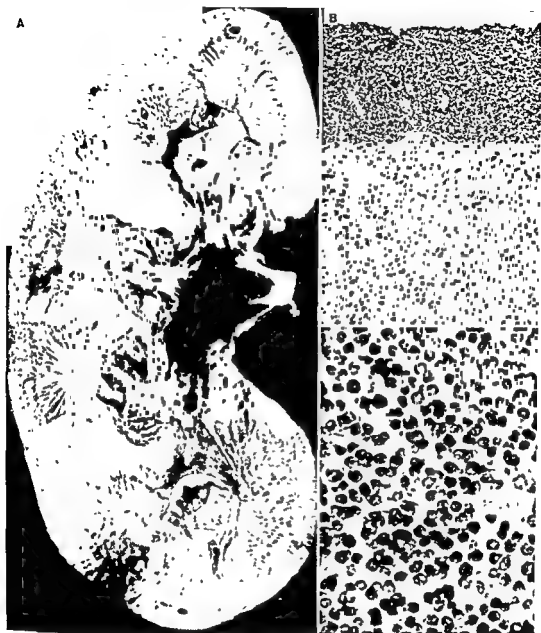


FIG. A. *Myelogenous leukemia* with grey and hemorrhagic areas of leukemic infiltration. The pelvis is discolored by spontaneous intramucosal hemorrhage which may simulate neoplasms on pyelography.

FIGS. B AND C. *Myelogenous leukemia* in low and high power magnification respectively. Figure B superficially simulates subacute pyelonephritis. Detailed study of the cells under higher magnification reveals their leukemic nature.

PLATE 319. MALIGNANT NEOPLASMS: MYELOGENOUS LEUKEMIA



FIG A *Myelogenous leukemic infiltrate in interstitium of kidney showing pleomorphism, granularity of cytoplasm and mitotic activity*

FIG B *Myelogenous leukemia simulating sub-acute proliferative glomerulonephritis. The increased glomerular cellularity is due to the presence of leukemic cells in the glomerular capillaries.*

FIG C *Hyaline granules in the epithelium of the proximal tubules in association with leukemic infiltrate. This hyaline granule nephrosis is identical with that in other conditions.*

FIGS D AND E *Fibrinoid degeneration of afferent arterioles and interlobular arteries is occasionally found in leukemic kidneys and is unrelated to hypertension or systemic vascular sclerosis. This change has been attributed to P<sup>3</sup> (Platt) which was used in this case.*



FIGS A AND B Lymphatic leukemic infiltration of kidneys

FIG C Lymphatic leukemic infiltration superficially simulating acute diffuse interstitial nephritis. The glomeruli and tubules, although surrounded by the leukemic infiltrate, seem to be structurally intact. Despite the extensive leukemic involvement of the kidneys, there was no renal insufficiency, this is almost always the case.

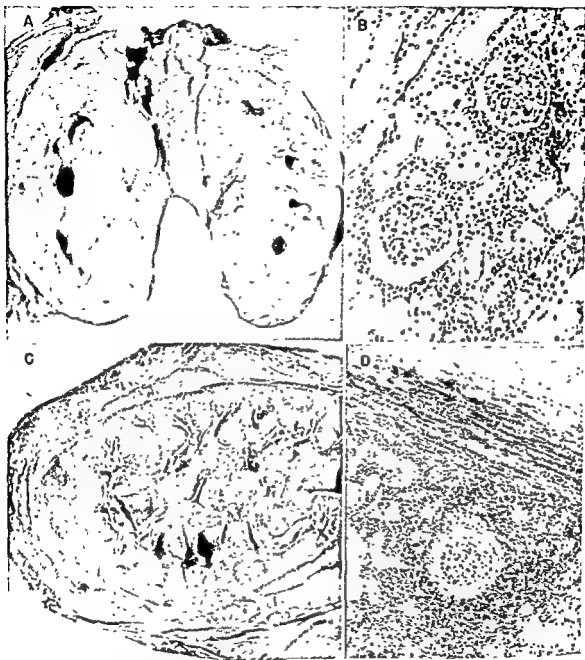


FIG A. *Lymphosarcomatous infiltration of renal parenchyma and perirenal tissues*

FIG C *Lymphosarcomatous envelope tightly wrapped about kidney. The parenchyma is also involved*

FIG B. *Periglomerular and interstitial lymphosarcomatous infiltrate.*

FIG D *Lymphosarcomatous infiltrate of parenchyma and capsule with some resemblance to a focus of subacute pyelonephritis.*

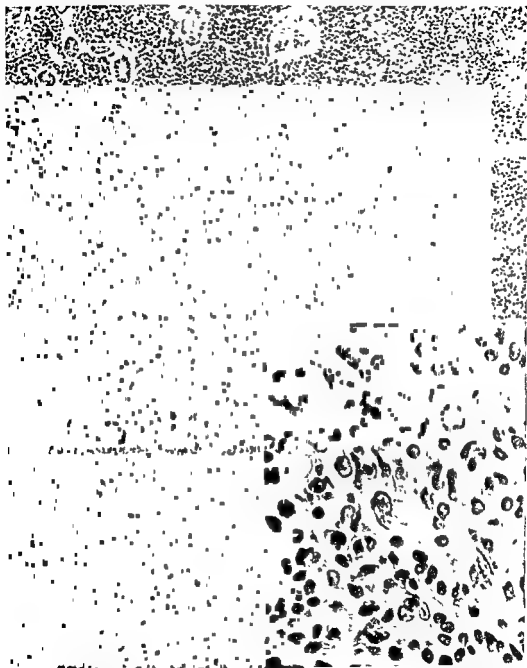


FIG A *Lymphosarcomatous infiltrate* with preservation of tubular structure. The histologic picture is quite like that of lymphatic leukemia.

FIG B *Mycosis fungoides*, a small focus in the kidney. This is a most unusual finding in proved cases of mycosis fungoides.

FIG C *Mycosis fungoides*, a higher magnification of figure B, showing the pleomorphism of the infiltrate.



phasize that the failure to find infiltration is no insurance of survival. In a series of McDonald and Priestley, only 13 of 25 patients with such tumors survived five years. In other words, the noninfiltrating papillary tumors of the renal pelvis, that is, the "papillomas," are of far greater concern than the corresponding tumor of the urinary bladder. Since approximately half of the patients with renal "papillomas" do not survive five years, it appears likely that by the time the tumor has been removed, infiltration has already occurred. The difficulty is that histologic evidence of infiltration may be completely masked in a given section. The case illustrated in plate 312 emphasizes this feature rather strikingly. Hence, the "papilloma" of the renal pelvis had better not be regarded as a benign lesion from the practical viewpoint.

The prognosis of the remainder of the pelvic tumors is especially poor. In the series of McDonald and Priestley, 3 of 18 patients with the obviously infiltrating papillary carcinomas, survived five years or longer, and only 1 of 14 patients having nonpapillary lesions was alive after five years. Higgins in 1939 was unable to find a single reported instance of five year survival of a case of squamous cell carcinoma of the renal pelvis. The over-all prognosis for tumors of the renal pelvis is therefore far worse than for those of the parenchyma.

#### MUCOUS ADENOCARCINOMA OF THE RENAL PELVIS

##### Definition

Inasmuch as the renal pelvis as well as the ureter and bladder is lined by stratified transitional cell epithelium, most of the neoplasms arising from the renal pelvis are expected to be of the transitional or squamous cell types. Metaplasia of the normal transitional epithelium into the squamous cell pattern is a common reaction in the presence of infection or stones which are frequently found with pelvic tumors. A similar metaplasia occurs in other organs such as the urinary bladder, the gall bladder and the lungs. However, the prosoplastic conversion of the transitional cell epithelium of the renal pelvis into the more specialized, mucus producing epithelium of the type that occurs

in the colon, is an exceedingly rare phenomenon. By this same token, mucous adenocarcinomas of the renal pelvis are correspondingly rare.

Up to 1950, only two instances of mucous adenocarcinoma of the renal pelvis had been reported (Ragins and Rolnick, Ackerman) and a third case of mucinous metaplasia of the pelvis and part of the ureter is on record (Plaut). The ages of the patients with carcinoma were 51 and 66, the patient with simple metaplasia was 58 years old. Hydronephrosis with chronic pyelonephritis was present in all three cases, calculi were noted in all of the cases, metastasis occurred in one case (Ackerman).

The histologic picture of the carcinoma is identical with those that arise from the vestigial urachal cysts at the fundus of the bladder and is indistinguishable from gelatinous or mucous adenocarcinomas of the large intestine (plate 315). There is a temptation to indulge in the discussion of the possibly dysontogenetic nature of the intestinal type of glandular epithelium within the renal pelvis. Actually this is the same kind of epithelium that is commonly found in the urinary bladder with ectrophy. In this circumstance, the alteration is logically assumed to be the result of the exposure of the mucous membrane of the ectrophied bladder to adverse conditions with which it is not "intended" to cope. The calculi and infections may similarly provoke a change to mucus producing epithelium in the pelvis, instead of the expected epidermalization, in rare instances.

The origin of mucus producing intestinal type of epithelium from Brunn's glands or from pyelitis cystica are other possibilities that could be invoked. However, an examination of the altered renal mucosa indicates a thorough, intrinsic conversion of the entire epithelium in the involved areas rather than a mucous conversion merely of cysts of the Brunn's nests or of the intraepithelial foci of pyelitis cystica (plate 190).

#### PARARENAL TUMORS

In view of the variety of pararenal tumors that occurs, it appears that the pararenal tissues have a greater propensity for neoplastic pro-

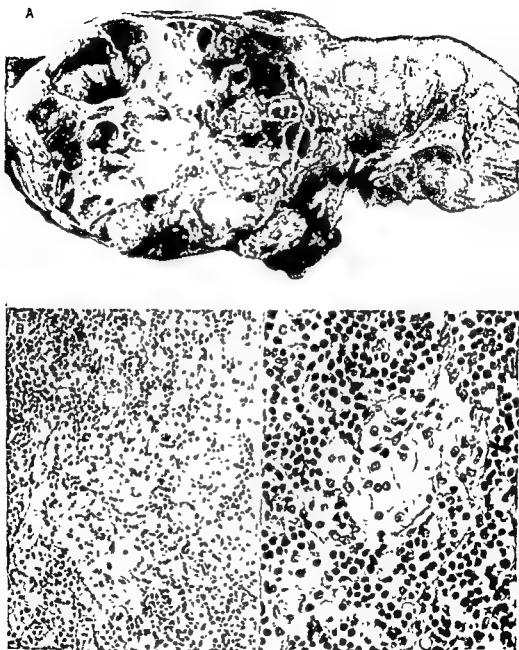


FIG. A. Adenocarcinoma (clear cell), intimately combined with lymphosarcoma, an unusual occurrence further illustrated below. The patient had generalized lymphosarcomatosis.

FIGS. B AND C. Clear cell adenocarcinoma admixed with lymphosarcoma. These sections are from the tumor illustrated in figure A.

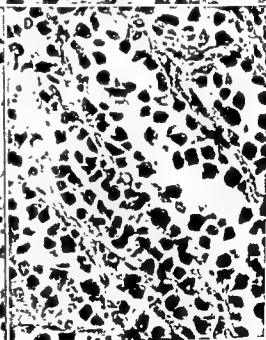
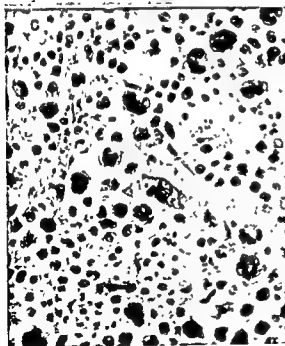
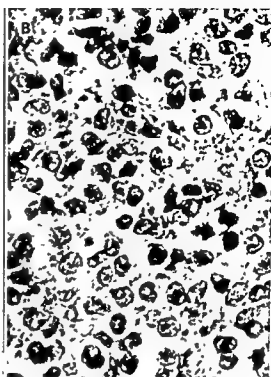


FIG A *Reticulum cell sarcoma* of kidney (grey focus—arrow)

FIG C *Giant reticulum cell sarcoma* which may be indistinguishable from Hodgkin's sarcoma in a single section

FIG B *Typical pattern* of fairly uniform reticulum cell sarcoma of kidney.

FIG D *Reticulum cell sarcoma* of kidney in an atypical pattern, and therefore, easily confused with adenocarcinoma

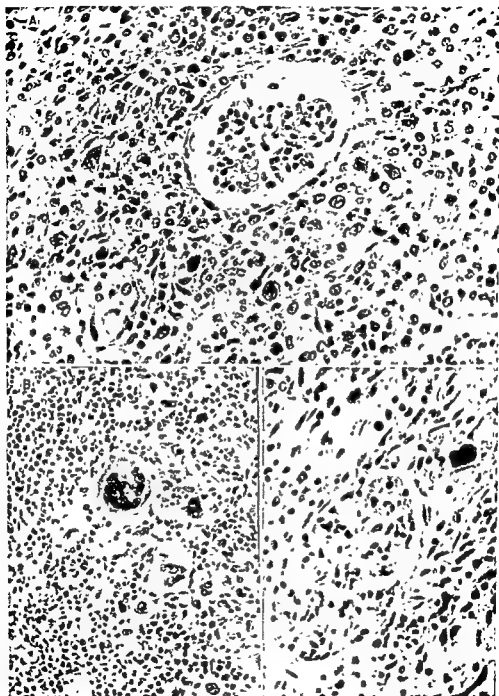
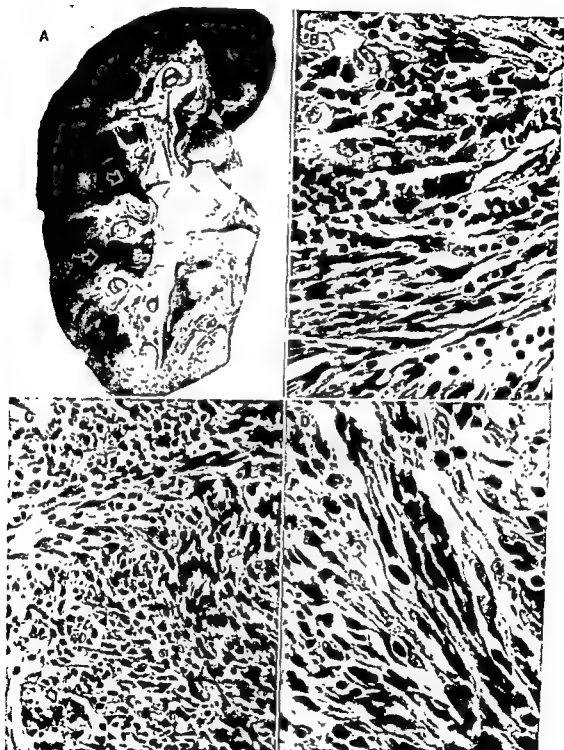


FIG. A. *Hodgkin's sarcoma of kidney*

FIG. B. *Hodgkin's granuloma of kidney*

FIG. C. *Hodgkin's granuloma of kidney*



FIGS. A, B, C AND D Variants of Kaposi's sarcoma showing abortive blood vessels lined by neoplastic cells, granules of hemosiderin and anaplastic compact spindle cells. Gross nodules are shown in figure A (arrows)

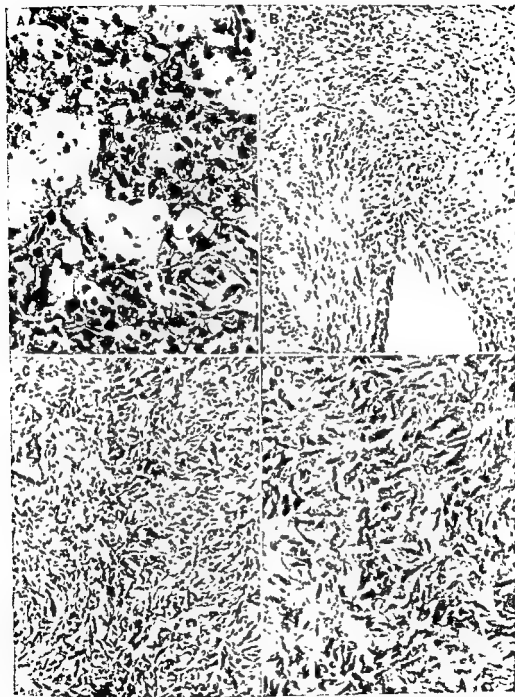


FIG. A Angiosarcoma with many lipid histiocytes

FIG. B Another section of the angiosarcoma of figure A. Metastasis from this type of neoplasm is most unlikely

FIGS. C AND D Hemangioepithelioma of kidney with metastases in pituitary gland and liver (biopsies). No cutaneous lesions were present. The question of site of origin of this tumor was not settled in this case in which no autopsy was performed

liferation than the tissues surrounding other viscera with the possible exception of the lung. The tissues normally consist of adipose, fibrous, vascular, muscular and neural elements and corresponding tumors of these tissues occur. There are lipomas, fibromas, myxomas, angiosarcomas, lymphangiomas, and compounded tumors such as angiomylipomas, fibrolipomas, myxolipomas as well as their sarcomatous counterparts (plates 316, 317). Pararenal teratomas occur rarely (Campbell, Baker and Ragins). Metaplastic ossification or chondrification may be mistaken for teratomatous components. The most common of the pararenal tumors are the various lipomas (Pemberton and McCaughan). Occasionally, a pararenal lipoma may so distort the renal pelvis as to suggest an intrapelvic tumor. Neoplasms may arise from perinephric tissues which seem not to be indigenous to this region but which are in reality metaplastic derivations. The osteogenic sarcoma pictured in plate 330 is a case in point. Other examples of extra-osseous osteogenic sarcoma have been recorded (Binkley and Stewart; Weber). They are relatively benign tumors. As already mentioned, some of the largest neoplasms of the entire body have originated from the perinephric tissues and have reached weights of 60 to 69 pounds (Gordon-Taylor). The symptoms have been those resulting from compression.

It is curious that there is a higher incidence of pararenal tumors among females than males. The ratio in von Wahlendorf's series was 106 females to 42 males. The tumors may be found at all ages and both sides are affected equally. Local recurrences following operative removal are more common than would be anticipated from the histologic picture of some of the tumors, although portions of a lipoma may undergo sarcomatous degeneration (plate 317B), at least in the purely histologic sense.

### *Peripelvic Lymphatic Cysts*

#### *Solitary*

Solitary peripelvic cysts have been called "lymphatic cysts" by some observers. These are rare and usually small, although huge ones with a volume of one to five liters have been described. The larger ones obviously would cause symptoms of compression. In several in-

stances, hypertension has been attributed to ischemia caused by the pressure of the cyst on the renal vessels. Removal or drainage of a cyst in these cases is said to have been followed by a sustained fall in blood pressure (Schäfer and Kreutzmann).

#### *Multicystic*

In addition to the solitary cysts, there occur multiloculated or honey-combed hilar, peripelvic, pericalyceal or pyramidal cysts (plate 316A). These cysts are not rare, occurring over 1 per cent of routine autopsies in patients from 17 to 71 years of age and about four times as commonly in males as in females (Henthorpe). The majority of the patients in Henthorpe's series had some associated obstructive or inflammatory disease of the kidney including nephrolithiasis, pyelonephritis and prostatic hypertrophy. On this basis, acquired obstructive lymphangiectasis might be considered the most likely pathogenesis of the cysts. If obstruction of lymphatic drainage is the cause of lymphangiectasis, it is surprising that many more examples are not found especially in the cases of extensive cancerous compression of ureteral and renal lymphatics. However, 8 of the 20 cases had associated, possibly congenital malformations, some of which were probably embryogenetically much alike, these included pancreatic and hepatic cysts, hemangioma of the ileum, liver and spleen, and "lymphangioma" of the spleen. Nevertheless, the observation that these cysts mostly beyond the second decade of life suggests an acquired rather than congenital origin. As with cysts elsewhere in the kidney and in other organs, the theories of genesis run the gamut of dysontogenetic manipulation, of which the theory of origin from remnants of the wolffian body appears to have won many adherents.

The multiple cysts may be visible, without sectioning the kidney, as bowcatted masses about the size of lymph nodes lobulating the peripelvic fat. The photograph in Henthorpe's paper demonstrates this feature well. The sectioned surface reveals pelvic or pericalyceal thin-walled cysts varying in size from those barely detectable to some 5 cm in diameter, but averaging about 1 cm. The lining of the cyst

PLATE 328. MALIGNANT NEOPLASMS. METASTATIC TUMORS

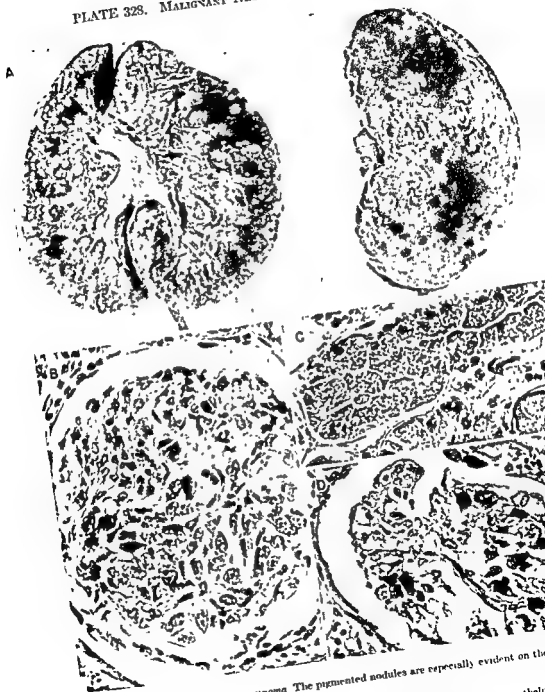


Fig A Metastatic melanocarcinoma. The pigmented nodules are especially evident on the  
1st surface.

Fig C Melanin granules in epithelial  
convoluted tubules in a case of widely  
pigmented melanocarcinoma

Fig B Pigmented metastasis of melanocarcinoma.

Fig D Metastatic cells of melanocarcinoma  
in capillaries (Compare with Fig A)



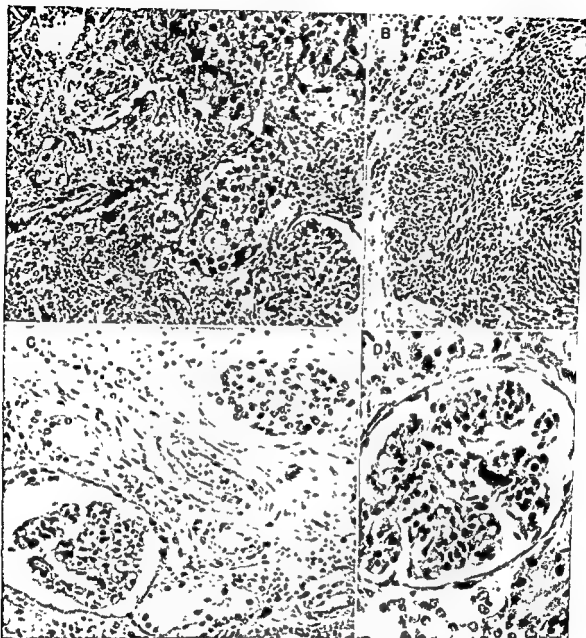


FIG A Metastatic choriocarcinoma to kidney. Langhans and syncytial cells and the hemorrhagic character of the tumor are noted.

FIG C Metastatic epidermoid carcinoma (from the ureter) within a renal lymphatic vessel.

FIG B Metastatic epidermoid carcinoma from the lung, which may be mistaken for a primary, renal pelvic carcinoma (plate 311B).

FIG D Megakaryocyte within a glomerular capillary, a common finding not to be confused with a metastatic cancer cell.

PLATE 330 MALIGNANT NEOPLASMS EXTRA-OSSEOUS OSTEOGENIC SARCOMA



FIG. A Extra-osseous osteogenic sarcoma originating in the perirenal tissue

FIG. B Perirenal osteogenic sarcoma with foci osteogenesis and spindle cell areas

FIGS. C AND D Perirenal extraosseous osteogenic sarcoma with new bone and giant cell formation in a malignant stroma. There were no metastases. The extraosseous osteogenic sarcomas in general, have a far better prognosis than those arising within bones

PLATE 331 · MALIGNANT NEOPLASMS: MULTIPLE MYELOMA

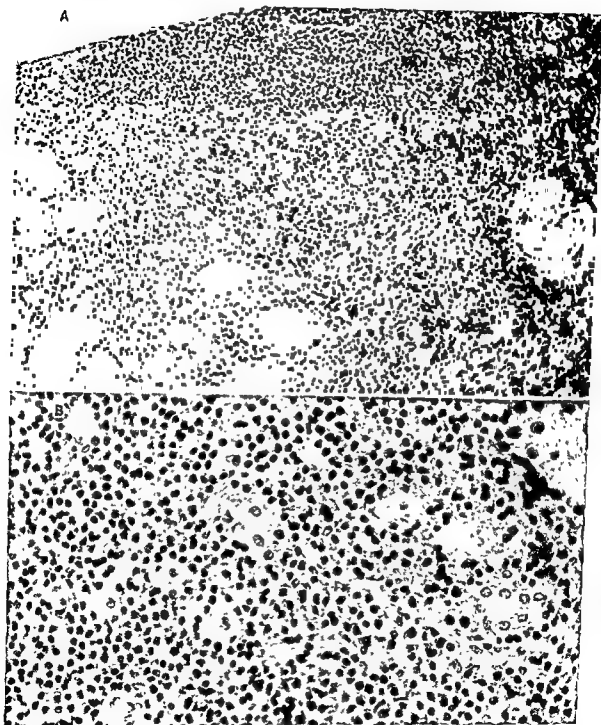
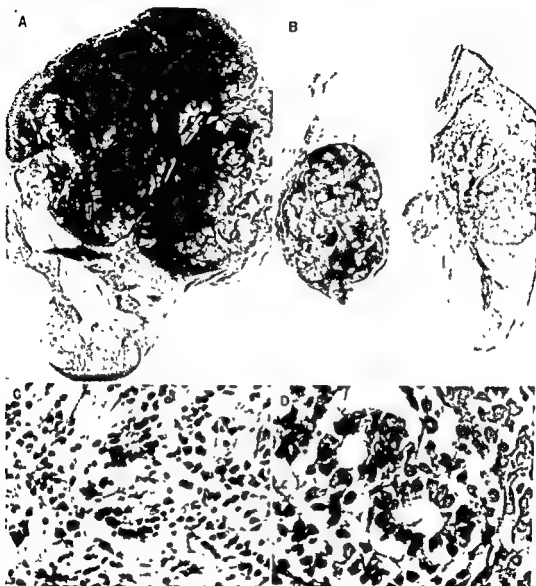


FIG A *Myelosarcomatous (multiple myeloma, plasmacytoma) growth within kidney from a case of widespread myelomatous involvement of bones*

FIG B *Myeloma (plasmacytoma) of kidney of figure A under higher magnification. There was no evidence of myeloma nephrosis in this case. (Compare plates 149-151.)*



FIGS A AND B Adrenal neuroblastoma directly invading the adjacent renal parenchyma and easily mistaken for a primary renal neuroblastoma

FIG C True rosettes of an adrenal neuroblastoma

FIG D Tubular structures of a Wilms' tumor simulating true rosettes for which they may be mistaken

is smooth and the contents comprise a clear serous fluid. Nothing concerning the position of the cysts in anatomic relation to blood vessels militates against their lymphatic nature. Histologically, the wall of the cysts is made up of flattened lining cells about which there is a thin rim of fibrous tissue or smooth muscle, as in a vein or lymphatic. In the three cases we have personally seen, we were not able to know from the histologic sections whether or not the cysts were dilated lymphatics or veins. It is also to be noted that there occur isolated multilocular peripelvic cysts which appear to be dilated isolated foci of tubules or tubular remnants rather than lymphatic cysts.

### *Lymphangioma*

A true lymphangioma, to be distinguished from lymphangiectasis, or multiloculated lymphatic cysts, is a rare pararenal tumor. The case reported by Kretschmer and Hibbs in 1934 is an excellent example of an encapsulated lymphangiomatous tumefaction about the size of an orange ( $11 \times 9 \times 8.5$  cm.) which markedly distorted the kidney by compression. The patient was 59 years of age. At that time, they were able to find two other reports of such tumors adjacent to the kidney.

### PARARENAL HEMATOMA

Pararenal hematoma results from spontaneous rupture of a sclerotic aorta (plate 316C) or main renal artery with or without prior aneurysmal dilatation, massive adrenal hemorrhage (adrenal "apoplexy"), hemorrhage from retroperitoneal tumors, blood dyscrasias, trauma, and from extensions of intrarenal hemorrhage secondary to periarthritis nodosa (plate 228B), lithiasis, hydronephrosis, infarcts, cysts and neoplasms. In some instances, the cause of the hemorrhage escapes detection.

The onset of the pararenal hematoma is characterized by sudden, severe, intermittent, shooting pain in the flank followed often by

intra-abdominal catastrophe, renal lithiasis, cholelithiasis, or perforation of the gallbladder.

### METASTASIS

The kidney is a relatively common site for the deposit and propagation of metastases. Those primary tumors that are prone to give rise to widespread metastases, are likely also to seed foci in the kidney. Among such tumors are bronchogenic carcinomas (plate 329B), malignant melanomas (plate 328), choriocarcinomas (plate 329A) and the various lymphomas (plates 318-325). These may rarely involve the renal pelvis in addition to the parenchyma. However, the kidney receives metastases also from many other primary neoplasms, including especially those from breast, pharynx, larynx, opposite kidney, thyroid, stomach, skin, pancreas, liver, esophagus, large intestine, adrenal neuroblastoma and others. The adrenal gland (33 per cent), lungs (18 per cent), thyroid gland (15 per cent) and opposite kidney (12 per cent) are the chief sources of metastasis. The routes of spread of tumors to the kidney are:

1. Direct contiguous invasion
2. Lymphatic (retrograde)
3. Venous (retrograde)
4. Arterial

The organs responsible for direct spread of cancers to the kidney include stomach, pancreas, adrenals (with cortical and medullary tumors) (plate 332), and large intestine. Occasionally, the kidney may be invaded by direct extension from an adjacent lymph node which is itself occupied by some metastatic lesion. As in other regions in which there is a tough fibrous capsule, the renal capsule may effectively bar the penetration into the renal parenchyma of even highly anaplastic pararenal cancers.

Invasion of the kidney by retrograde permeation of the lymphatic vessels is especially common with anaplastic epidermoid carcinoma of the renal pelvis. The lymphatic deposits in this instance may be so atypical as to simulate adenocarcinoma, reticulum cell sarcoma, myosarcoma or Wilms' tumor (plate 311B). Such extensive intrarenal lymphatic spread may be seen also in cases of carcinoma of the stomach,

clinical differential diagnosis may be difficult to make since the picture may simulate an



FIG. A Adrenal neuroblastoma metastatic to kidney.

FIG. B True rosettes of a metastatic adrenal neuroblastoma.

FIGS. C AND D Wilms' tumor with multinucleated giant cells deceptively similar to true rosettes.

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PLATE 333. MALIGNANT NEOPLASMS: METASTATIC TUMORS



FIG. A. Adrenal neuroblastoma metastatic to kidney.

FIG. B. True rosettes of a metastatic adrenal neuroblastoma.

FIGS. C AND D. Wilms' tumor with multinucleated giant cells deceptively similar to true rosettes.

PLATE 334. ADRENAL TUMORS

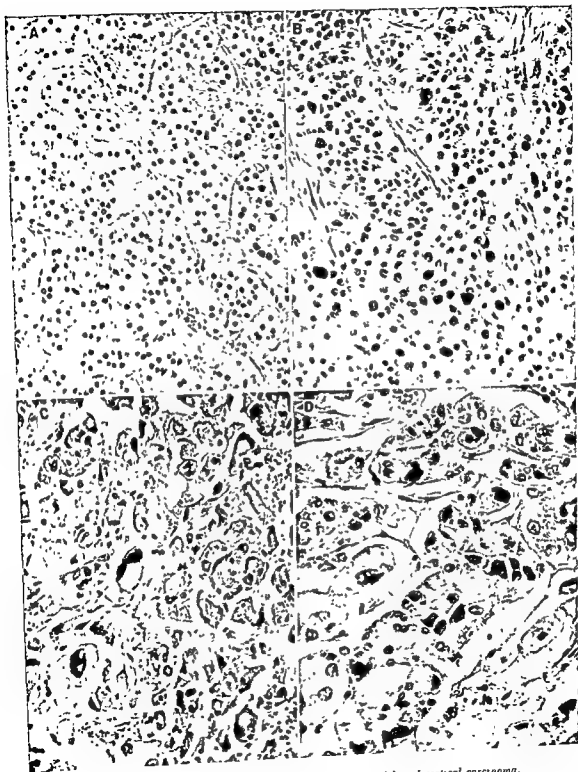


FIG A Adrenal cortical adenoma

FIG C Pheochromocytoma of adrenal medulla

FIG B Adrenal cortical carcinoma.

FIG D Renal adenocarcinoma simulating a pheochromocytoma

pancreas, lung, and gall bladder. The lymphatic invasion may be so complete in these instances as to indicate the actual anatomical pattern of the renal lymphatics (Peirce).

*Retrograde invasion of renal veins and their intrarenal tributaries* has been observed with ovarian and contralateral renal carcinomas and with other neoplasms which have extended first into the inferior vena cava. *Arterial embolic metastases* are of frequent occurrence. They may be so large as to occlude a major branch and thereby produce an infarct. Frequently, arterial metastases lodge within glomerular capillaries and, when sparse, may easily be overlooked (plate 328B). As a rule, the metastatic foci are visible grossly as spherical, lentiform or rhomboidal nodules of various sizes. The non-spherical metastases tend to have their longer axis parallel to the rays of the kidney because of the natural cleavage planes; others may have their shape moulded into a pyramidal or conical form by the limitation of the capsule (Wilks). Metastases rarely reach very large dimensions,

and, in part for this reason, they infrequently undergo extensive spontaneous necrosis. Incidentally, metastatic foci of adenocarcinoma may lodge in Bowman's space and be misinterpreted as hyperplastic and hypertrophic parietal epithelium of Bowman's capsule.

It is remarkable that despite overwhelming involvement by metastases, or particularly lymphomas, the function of the kidney is rarely seriously compromised thereby. Histologically, the glomerular and tubular structures may appear quite intact though enveloped by neoplastic tissue (plate 325). It is extremely uncommon, for example, for patients with massive parenchymal lymphomatous infiltrate in the kidney to develop an associated hypertension even though one might anticipate an ischemic compression of small renal arteries and arterioles by the tumor. Infrequently a large metastasis at the renal hilum encroaches on the main vessels, or a metastatic lesion obstructing the ureter may play a part in the development of hypertension or hydronephrosis.

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# 15. Histologic Artefacts

A CLEAR understanding of the nature, mechanism of production, and differential histologic diagnosis of artefacts is frequently of considerable importance. The misinterpretation of factitious changes has led to a number of erroneous conclusions some of which are fixed in the literature. Many of these artefacts may be found in any organ, several of them, however, are limited to the kidney. Most of the more significant ones are herein described and illustrated.

## Glomeruli

Bowman's spaces occasionally appear abnormally enlarged and the tufts so conspicuously compressed as to simulate hydronephrotic atrophy simply as a result of shrinkage caused by formalin fixation, caution should be observed in the estimation of glomerular cellularity in thick paraffin sections and especially in frozen sections of kidneys. The disparity between the cellularity of glomeruli in frozen sections in contrast with that of thin (4-6 microns) paraffin sections may be more striking than anticipated. Hence, the diagnosis of acute diffuse glomerulonephritis made on the basis of a frozen section at autopsy, may have to be retracted when the thin paraffin section is available.

Another feature of poor fixation—particularly with formalin—is the tendency of the cytoplasm of the endothelial cells of the glomerular capillaries to swell and merge so as to give the impression, as a result of their acidophilic syncytium, that the basement membranes of the glomerular capillaries are thickened when they are actually normal.

More recently, significance has been attached to the so-called herniation of tubules into the glomerular or Bowman's space. It is admitted that in none of these instances is there evidence of embarrassment or alteration of the normal physiology or histology of the malpighian tuft such as would be expected by this sort of encroaching "lesion." Therefore, the artefactual genesis of this picture seems settled.

## Tubules

One of the problems of the evaluation of alteration of tubular epithelium is the distinction between true degeneration and postmortem autolysis. Frequently, the change in the epithelium of the proximal convoluted tubules is labeled "necrotizing nephrosis," "infarct" or "ischemic necrosis" when the change is merely the result of postmortem alteration. The labile granular epithelium of the proximal tubules is more quickly after death than any nephron (plate 337 infarction, the protergo necrotic c tubular system of tubular epithelium necrosis tubular cell there is a u shadowy are of no regeneration intensifying base defin base the cyt S tubu cylin membr form artefa thelial the aci which re but which probably t tion of acti

The artefact is certain except in

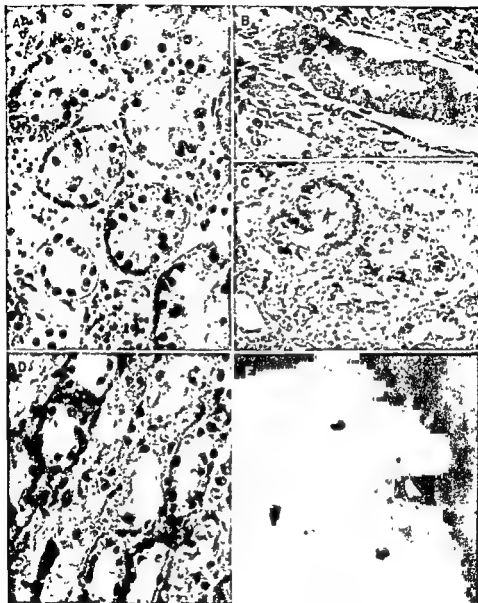


FIG A Formalin pigment in basilar portion of fatty epithelium of proximal tubules

FIG D Silver granules are to be differentiated from formalin pigment. This example of renal argyrosis was the result of the ingestion of silver nitrate

FIG B Formalin pigment in distal convoluted tubule

FIG C Hemosiderin in proximal tubules is to be differentiated from formalin pigment

FIG E Refractile foreign bodies, such as dust in or upon the section, are to be differentiated from crystals deposited in vivo

PLATE 336. HISTOLOGIC ARTEFACTS OF KIDNEY

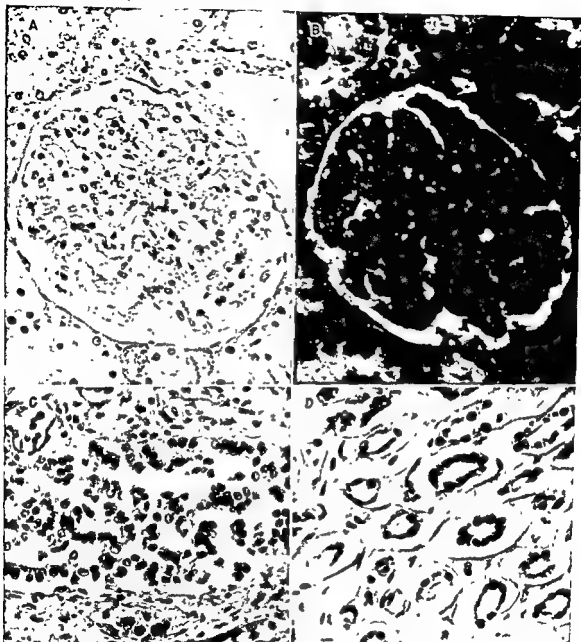


FIG A Formalin pigment in a glomerulus

FIG C Postmortem epithelial desquamation

FIG B Refractile formalin pigment in glomerulus of figure A

FIG D Postmortem shrinkage of epithelium from the tubular basement membrane (Formalin fixation)

PLATE 337. HISTOLOGIC ARTEFACTS OF KIDNEY



FIG. A Postmortem degeneration of epithelium of proximal convoluted tubules. The more resistant glomeruli and the epithelium of the distal convoluted tubules survive a longer period. The bland nonreactive disappearance of nuclei is characteristic of this phenomenon of postmortem change.

FIG. B Uneven staining reaction is due to an oily contaminant on the surface of the section or in the staining solutions.



FIG A Postmortem growth of bacteria in glomerular capillaries. Inflammatory reaction is absent.

FIG B Postmortem colonization of staphylococci in peritubular capillaries.

FIG C Postmortem growth of monilia.

FIG D. "Cysts" due to postmortem accumulation of gas from growth of *Cl. welchii*.

FIG E Antemortem septic embolus to afferent arteriole showing leukocytic reaction.

PLATE 339. HISTOLOGIC ARTEFACTS OF KIDNEY



FIG A Postmortem sloughing of endothelial nuclei into lumen of an artery. The elongated cells simulate fibroblasts

FIG B Artefactually implanted tumor cells in lumen of a vessel

FIG C Factitious invagination of wall of elastic retractile artery may be mistaken for a thrombus

FIG D Blue black mercury pigment from Zenker's fixative may be confused with calcium

FIG E Artifactual pseudonecrosis

phenomenon." Because of the retractility of muscular, elastic arteries, their cut ends frequently telescope or invaginate so that when sectioned, they may histologically simulate true thrombosis so closely as to be fixed in the literature in this disguised form. This artefact should be recognized in the routine hematoxylin and eosin stained sections, but a simple van Gieson elastic tissue stain positively reveals the elastic lamina and media indicative of the artificial invagination which, in the past, has been labeled "a peculiar smooth muscle thrombus" (plate 339C).

Another less camouflaged artefact is that caused by the spindled endothelial cells and muscle cells of the media which have been forced into the lumen of arteries by the knife of the microtome (plate 339A). Such cells in the midst of blood and fibrin simulate fibroblasts and may be mistaken for organizing thrombi.

Frequently red blood cells, in veins particularly, may appear sickled to the degree shown in plate 339E. Precisely why this distortion occurs is not entirely clear, but its association with local anoxia merits further thought and investigation.

### *Special Stains*

One of the most important bases for errors in the estimation of histologic changes in the kidney is the evaluation of special stains. Two principal types of errors are involved. In one, the misjudgment results from the artefactual precipitation of the stain in adventitious locations. For example, the red carmine granules of the Best's stain for glycogen, the blue masses of the ferri-ferrocyanide or Prussian blue reaction for iron or hemosiderin, or the granules of reduced silver compounds may be precipitated unnaturally and may easily be mistaken for intravital reactions. Similarly the localization of the various black sulfides ordinarily presumed to be reflective of the content of phosphatase, lipases or esterases (plate 24), may be varied by many artificial influences including heat, mechanical factors, and inhibiting chemical agents.

Not the least source of error is the brown to black granules of "formalin pigment." Formalin pigment appears to result from a reaction of formalin with hemoglobin and is deposited in organs fixed excessively long in solutions of formaldehyde. The pigment is deposited particularly within or about areas of congestion as well as within lipid foci (plate 335). In glomeruli, the formalin may be mistaken for malaria pigment (plate 336A, B); in tubules, it closely approximates hemosiderin, melanin, or the lipochromes. Of course, the stains for iron are negative in the case of formalin pigment. Moreover, this pigment is most often birefringent (plate 336B), and can usually be bleached in sections treated with sodium carbonate. Melanin may be bleached with permanganate or stained with silver. The lipochromes of the kidney are sudanophilic. With regard to the property of birefringence, it is to be borne in mind that particles of foreign matter caught within or above the section of tissue during its preparation, may also be anisotropic (plate 337E).

Occasionally, irregular areas of tissue may show no affinity for stains (plate 337B). This phenomenon may be due to the presence of droplets of an oily material on the section itself or actually contaminating oils within the aqueous staining solutions.

### *Postmortem Bacterial Invasion*

Occasionally it becomes a problem to distinguish between antemortem and postmortem colonization of bacteria. The criterion that is of obvious importance is the presence or absence of inflammatory cellular reaction about the bacteria (plate 338). However, in cases of agranulocytosis or severe neutropenia, antemortem accumulations of bacteria may occur with little or no reaction. *B. welchii* invasion after death or even terminally prior to death is characterized by the presence not only of the large bacilli but of the spaces from the gas generated by the bacteria (plate 338). Monilial infection (plate 338) is particularly common in cases treated with nitrogen mustards, and may occur antemortem without appreciable inflammatory reaction (plate 338).

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